

F2

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/101045 A2(51) International Patent Classification⁷: **C12N 15/12**,
C07K 14/705, C12N 5/10, C12Q 1/68, C07K 16/18,
G01N 33/50, 33/53

(21) International Application Number: PCT/EP02/06520

(22) International Filing Date: 13 June 2002 (13.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/297,835	13 June 2001 (13.06.2001)	US
60/351,238	22 January 2002 (22.01.2002)	US
60/352,914	29 January 2002 (29.01.2002)	US
60/357,161	12 February 2002 (12.02.2002)	US
60/381,086	15 May 2002 (15.05.2002)	US
60/381,739	16 May 2002 (16.05.2002)	US

(71) Applicants (for all designated States except US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH). **IRM LLC** [US/—]; PO Box HM 2899, Hamilton HM LX (BM).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PATAPOUTIAN, Ardem** [US/US]; 4330 North Talmadge Drive, San Diego, CA 92116 (US). **SONG, Chuanyzheng** [CN/US]; 87 Reinman Road, Warren, NJ 07059 (US). **GANJU, Pamposh** [GB/GB]; Novartis Institute for Medical Sciences, University College, 5 Gower Place, London WC1E 6BN(GB). **PEIER, Andrea** [US/US]; 9725 Mesa Springs Way 176, San Diego, CA 92126 (US). **MCINTYRE, Peter** [AU/GB]; Novartis Institute for Medical Sciences, University College, 5 Gower Place, London WC1E 6BN (GB). **BEVAN, Stuart** [GB/GB]; Novartis Institute for Medical Sciences, University College, 5 Gower Place, London WC1E 6BN (GB).(74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW.(84) Designated States (*regional*): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: VANILLOID RECEPTOR-RELATED NUCLEIC ACIDS AND POLYPEPTIDES

(57) Abstract: This invention provides novel genes and polypeptides of the VR family, identification of $trkA^+$ pain specific genes expressed in the DRG, and use of these genes and polypeptides for the treatment of pain and identification of agents useful in the treatment of pain.

WO 02/101045 A2

VANILLOID RECEPTOR-RELATED NUCLEIC ACIDS AND POLYPEPTIDES

5 CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/297,835 filed on June 13, 2001, U.S. Provisional Application No. 60/351,238, filed on January 22, 2002, U.S. Provisional Application No. 60/352,914, filed on January 29, 2002, U.S. Provisional Application No. 60/357,161, filed on February 12, 2002, U.S. Provisional Application No. 60/381,086, filed on May 15, 2002, and U.S. Provisional Application No. 60/381,739, filed on May 16, 2002. These applications are incorporated herein by reference for all purposes.

COPYRIGHT NOTIFICATION

[0002] Pursuant to 37 C.F.R. 1.71(e), a portion of this patent document contains material which is subject to copyright protection. The copyright owner has no objection to the facsimile reproduction by anyone of the patent document or the patent disclosure, as it appears in the Patent and Trademark Office patent file or records, but otherwise reserves all copyright rights whatsoever.

BACKGROUND OF THE INVENTION

20 Field of the Invention

[0003] This invention pertains to novel vanilloid receptor (VR) related nucleic acids and polypeptides. In particular, the invention relates to proteins that are homologous to known VRs, nucleic acids encoding such proteins, identification of $trkA^+$ pain-specific genes, and the use of these genes and polypeptides in methods of diagnosing pain, methods of identifying compounds useful in treating pain and methods of treating pain.

Background

[0004] Pain has been defined as the sensory experience perceived by nerve tissue distinct from sensations of touch, pressure, heat and cold. Individuals suffering from pain

typically describe it by such terms as bright, dull, aching, pricking, cutting, burning, etc. This range of sensations, as well as the variation in perception of pain by different individuals, makes a precise definition of pain difficult. Pain as suffering, however, is generally considered to include both the original sensation and the reaction to that sensation.

- 5 Where pain results from the stimulation of nociceptive receptors and transmitted over intact neural pathways, this is termed nociceptive pain. Alternatively, pain may be caused by damage to neural structures, often manifesting itself as neural supersensitivity, and is referred to as neuropathic pain.

[0005] Neuropathic pain is a particular type of pain that has a complex and
10 variable etiology. It is generally a chronic condition attributable to complete or partial transection of a nerve or trauma to a nerve plexus or soft tissue. This condition is characterized by hyperesthesia (enhanced sensitivity to a natural stimulus), hyperalgesia (abnormal sensitivity to pain), allodynia (widespread tenderness, characterized by hypersensitivity to tactile stimuli) and/or spontaneous burning pain. In humans, neuropathic
15 pain tends to be chronic and debilitating, and occurs during conditions such as trigeminal neuralgia, diabetic neuropathy, post-herpetic neuralgia, late-stage cancer, amputation or physical nerve damage.

[0006] Most drugs including conventional opioids and antidepressants are not
practical against chronic pain such as neuropathic pain, either because they are not effective
20 or have serious side effects. For these reasons, alternate therapies for the management of chronic or neuropathic pain are widely sought.

[0007] Stimuli such as heat, cold, stretch, and pressure are detected by specialized sensory neurons within the Dorsal Root Ganglia (DRG). These neurons fire action potentials in response to these mechanical and thermal stimuli, although the molecular
25 mechanism for such detection is not known. Recently, two channels, vanilloid receptor 1 (VR1) and vanilloid receptor-like protein 1 (VRL1), have been isolated from DRG that respond to different thresholds of high heat, and hence act as pain receptors. These channels belong to a family of TRP channels that in *C. elegans* and *D. melanogaster* are involved in mechano- and osmoregulation.

30 [0008] The VR1 is a calcium channel with six transmembrane domains and a putative pore domain. The channel can be activated by many distinct reagents, including heat, low pH (high proton concentration is present during injury and inflammation), and

capsaicin (the active ingredient in hot chili peppers). The knockout of VR1 in mice has demonstrated that this channel plays a role in pain propagation; however, since the phenotype is rather subtle, it also implies that VR1 is not the sole receptor for high heat and pain. To date, one other homologue of VR1 is known in mammals - the VRL1. VRL1 is structurally very similar to VR1, but is expressed on DRG neurons that are not involved in pain reception (in contrast to VR1).

[0009] The somatic sensory neurons detect external stimuli such as heat, cold and noxious stimuli through the activation of thermal and mechanical receptors/channels. The VR family represents the first example of molecules expressed within the DRG that have such activation capabilities. Since these molecules are relatively specific to sensory neurons (for example, VR1 knockout mice do not have phenotypes outside of pain perception), they represent highly promising targets for developing drugs against pain or other thermal noxious stimuli. VR1 knockout mice have demonstrated that other molecules have to be involved in pain perception. However, despite the large amount of interest generated in the scientific community concerning this class of receptors, so far, no other receptors of this class have been identified.

[0010] In view of the role of the VR members in pain perception, the identification of new members of VR would allow the development of therapeutic candidates specifically designed to block these new TRP channels, which would enable the treatment of various disorders associated with chronic pain. In addition, the identification of new VR members would permit the screening of various drugs to identify those compounds suitable for further, in-depth studies of therapeutic applications.

SUMMARY OF THE INVENTION

[0011] The present invention relates to members of the VR family, in particular TRPV3 (previously known as VRLS, VRLX, VR4 and TRPV7), TRPV4 (previously known as VRL3 and OTRPC4) and TRPM8 (previously known as TRPX) nucleic acids and polypeptides, recombinant materials and methods for their production. In another aspect, the present invention relates to the identification of $trkA^+$ pain-specific genes expressed in the DRG. In yet another aspect, the present invention relates to methods for using the TRPV3, TRPV4, TRPM8 and $trkA^+$ pain-specific nucleic acids and polypeptides, including methods for treating pain, inflammation, skin disorders and cancer, methods of diagnosing pain,

inflammation, skin disorders and cancer, methods of identifying agents useful in the treatment of pain, inflammation, skin disorders and cancer and in methods of monitoring the efficacy of a treatment for pain, inflammation, skin disorders and cancer.

TRPV3

5 **[0012]** The invention provides isolated and/or purified TRPV3 nucleic acid molecules, such as: a) a polynucleotide that encodes a mouse TRPV3 protein comprising amino acid residues 1-791 of SEQ ID NO: 2; b) a polynucleotide that encodes a mouse TRPV3 protein comprising amino acid residues 2-791 of SEQ ID NO: 2; c) a polynucleotide that encodes a functional domain of a mouse TRPV3 protein; d) a polynucleotide that
10 encodes a human TRPV3 protein comprising amino acid residues 1-791 of SEQ ID NO 5; e) a polynucleotide that encodes a human TRPV3 protein comprising amino acid residues 2-791 of SEQ ID NO 5; f) a polynucleotide that encodes a functional domain of a human TRPV3 protein; and g) a polynucleotide that is complementary to a polynucleotide of a) through f). In some embodiments, the nucleic acid molecule is a) or b) and comprises a first
15 polynucleotide that is 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 3 (mouse TRPV3), or is d) or e) and comprises a first polynucleotide 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 6 (human TRPV3). The nucleic acids can be 90% or more, or 95% or more, identical to a second polynucleotide having a nucleotide sequence as
20 set forth in SEQ ID NO: 3 or SEQ ID NO: 6, or can be identical to the respective polynucleotide. Examples of TRPV3 nucleic acids of the invention include polynucleotides that are 80% or more, 90% or more, or 95% or more, identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 65-2440 of SEQ ID NO: 1 (mouse TRPV3) or nucleotides 57-2432 of SEQ ID NO: 4 (human TRPV3).

25 **[0013]** The invention also provides isolated TRPV3 nucleic acid molecules that encode polypeptides that include one or more functional domains of a mammalian (e.g., human or mouse) TRPV3 polypeptide. The polypeptides encoded by these nucleic acid molecules can include, for example, one or more functional domains such as ankyrin domains, transmembrane regions, pore loop regions, and coiled-coil domains. As an
30 example, the polypeptides can include a pore loop region flanked by two transmembrane regions, and/or four ankyrin domains.

[0014] Also provided by the invention are isolated and/or purified TRPV3 polypeptides. Such polypeptides include, for example, a) a mouse TRPV3 protein comprising amino acid residues 1-791 of SEQ ID NO: 2; b) a mouse TRPV3 protein comprising amino acid residues 2-791 of SEQ ID NO: 2; c) one or more functional domains of a mouse TRPV3 protein; d) a human TRPV3 protein comprising amino acid residues 1-791 of SEQ ID NO 5; e) a human TRPV3 protein comprising amino acid residues 2-791 of SEQ ID NO 5; and f) one or more functional domains of a human TRPV3 protein. For example, the TRPV3 polypeptides can include one or more functional domains selected from the group consisting of an ankyrin domain, a transmembrane region, a pore loop region, and a coiled-coil domain. In some embodiments, the polypeptides include a pore loop region flanked by two transmembrane regions, and/or four ankyrin domains.

[0015] Methods for identifying an agent that modulates TRPV3-mediated cation passage through a membrane are also provided by the invention. These methods involve: a) providing a membrane that comprises a TRPV3 polypeptide; b) contacting the membrane with a candidate agent; and c) determining whether passage of one or more cations through the membrane is increased in the presence of the candidate agent compared to passage in the absence of the candidate agent. In some embodiments, the membrane is a cell membrane and cation passage through the membrane is detected by measuring cation influx or efflux across the membrane into or out of the cell. The assay is conducted at a temperature of at least 33°C, in some embodiments. Also provided are methods in which a candidate agent that reduces cation passage is further tested for ability to treat pain by administering the candidate agent to a test animal and determining whether the candidate agent decreases the test animal's response to a pain stimulus. A pain stimulus can include, for example exposure to a temperature above 33°C.

[0016] The invention also provides methods for reducing pain associated with TRPV3 activity. These methods involve administering to a subject suffering from pain an analgesically effective amount of a compound that reduces TRPV3-mediated cation passage through a membrane or reduces signal transduction from a TRPV3 polypeptide to a DRG neuron. The pain can be with, for example, one or more of heat exposure, inflammation, and tissue damage. Suitable compounds can include, for example, an antibody that specifically binds to a TRPV3 polypeptide; an antisense polynucleotide, ribozyme, or an interfering

RNA that reduces expression of a TRPV3 polypeptide; and/or a chemical compound that reduces cation passage through a membrane that comprises a TRPV3 polypeptide.

[0017] Methods for determining whether pain in a subject is mediated by TRPV3 are also provided by the invention. These methods can involve: obtaining a sample from a region of the subject at which the pain is felt; and testing the sample to determine whether a TRPV3 polypeptide or TRPV3 polynucleotide is present and/or active in the sample. In some embodiments, the presence of a TRPV3 polypeptide in the sample is detected by determining whether cation passage across membranes of cells in the sample is mediated by a TRPV3 polypeptide. For example, TRPV3 involvement in mediating cation passage across membranes of the cells can be determined by detecting an increase in cation passage across membranes of the cells when assayed above 33°C compared to cation passage when assayed below 33°C. To distinguish between TRPV3 involvement in mediating cation passage and involvement by other ion channels (e.g., TRPV1 or TRPV2), the assay can be conducted at a temperature above the activation threshold of TRPV3 but below the activation threshold of the other receptor (e.g., below about 43°C or below about 52°C, respectively, for TRPV1 and TRPV2). As an alternative to assaying for TRPV3-mediated ion channel activity, one can detect the presence of a TRPV3 polypeptide in the sample by contacting the sample with a reagent that specifically binds to a TRPV3 polypeptide, or detect the presence of a TRPV3 polynucleotide in the sample by contacting nucleic acids from the sample with a test polynucleotide that can hybridize to a TRPV3 polynucleotide.

TRPV4

[0018] The invention also provides isolated TRPV4 nucleic acid molecules. These include, for example, a) a polynucleotide that encodes a mouse TRPV4 protein comprising amino acid residues 1-871 of SEQ ID NO: 14; b) a polynucleotide that encodes a mouse TRPV4 protein comprising amino acid residues 2-871 of SEQ ID NO: 14; c) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a mouse TRPV4 protein; d) a polynucleotide that encodes a human TRPV4 protein comprising amino acid residues 1-871 of SEQ ID NO 17; e) a polynucleotide that encodes a human TRPV4 protein comprising amino acid residues 2-871 of SEQ ID NO 17; f) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a human TRPV4 protein; and g) a polynucleotide that is complementary to a polynucleotide

of a) through f). In some embodiments, the nucleic acid molecule is a) or b) and comprises a first polynucleotide that is 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 15 (mouse TRPV4), or is d) or e) and comprises a first polynucleotide 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 18 (human TRPV4). The nucleic acids can be 90% or more, or 95% or more, identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 15 or SEQ ID NO: 18, or can be identical to the respective polynucleotide. Examples of TRPV4 nucleic acids of the invention include polynucleotides that are 80% or more, 90% or more, or 95% or more, identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 156-2771 of SEQ ID NO: 13 (mouse TRPV4) or to a nucleotide sequence as set forth in SEQ ID NO: 16 (human TRPV4).

[0019] The invention also provides isolated TRPV4 nucleic acid molecules that encode polypeptides that include one or more functional domains of a mammalian (e.g., human or mouse) TRPV4 polypeptide. The polypeptides encoded by these nucleic acid molecules can include, for example, one or more functional domains such as ankyrin domains, transmembrane regions, pore loop regions, and coiled-coil domains. As an example, the polypeptides can include a pore loop region flanked by two transmembrane regions, and/or three ankyrin domains.

[0020] Also provided by the invention are isolated and/or purified TRPV4 polypeptides. Such polypeptides include, for example, a) a mouse TRPV4 protein comprising amino acid residues 1-871 of SEQ ID NO: 14; b) a mouse TRPV4 protein comprising amino acid residues 2-871 of SEQ ID NO: 14; c) one or more functional domains of a mouse TRPV4 protein; d) a human TRPV4 protein comprising amino acid residues 1-871 of SEQ ID NO 17; e) a human TRPV4 protein comprising amino acid residues 2-871 of SEQ ID NO 17; and f) one or more functional domains of a human TRPV4 protein. For example, the TRPV4 polypeptides can include one or more functional domains selected from the group consisting of an ankyrin domain, a transmembrane region, a pore loop region, and a coiled-coil domain. In some embodiments, the polypeptides include a pore loop region flanked by two transmembrane regions, and/or three ankyrin domains.

[0021] Methods for identifying an agent that modulates TRPV4-mediated cation passage through a membrane are also provided by the invention. These methods involve: a)

providing a membrane that comprises a TRPV4 polypeptide; b) contacting the membrane with a candidate agent; and c) determining whether passage of one or more cations through the membrane is increased in the presence of the candidate agent compared to passage in the absence of the candidate agent. Cation influx and/or efflux can be measured as described above for TRPV3. In some embodiments, candidate agents that reduce cation passage are further tested for ability to treat pain by administering the candidate agent to a test animal and determining whether the candidate agent decreases the test animal's response to a pain stimulus.

[0022] Methods for reducing pain associated with TRPV4 activity are provided by the invention. These methods involve administering to a subject suffering from pain an analgesically effective amount of a compound that reduces TRPV4-mediated cation passage through a membrane or reduces signal transduction from a TRPV4 polypeptide to a DRG neuron. The compounds are suitable for treating, for example, neuropathic pain, and can include: a) an antibody that specifically binds to a TRPV4 polypeptide; b) an antisense polynucleotide, ribozyme, or an interfering RNA that reduces expression of a TRPV4 polypeptide; and c) a chemical compound that reduces cation passage through a membrane that comprises a TRPV4 polypeptide.

[0023] The invention also provides methods for determining whether pain in a subject is mediated by TRPV4. These methods involve obtaining a sample from a region of the subject at which the pain is felt, and testing the sample to determine whether a TRPV4 polypeptide or TRPV4 polynucleotide is present and/or active in the sample. The presence and/or activity of the TRPV4 polypeptide can be detected, for example, by determining whether cation passage across membranes of cells in the sample is mediated by a TRPV4 polypeptide, or by contacting the sample with a reagent that specifically binds to a TRPV4 polypeptide. One can detect the presence of a TRPV4 polynucleotide by, for example, contacting nucleic acids from the sample with a test polynucleotide that can hybridize to a TRPV4 polynucleotide.

TRPM8

[0024] Isolated and/or purified TRPM8 nucleic acid molecules are also provided by the invention. These TRPM8 nucleic acid molecules include, for example, a) a polynucleotide that encodes a mouse TRPM8 protein comprising amino acid residues 1-1104

of SEQ ID NO: 8; b) a polynucleotide that encodes a mouse TRPM8 protein comprising amino acid residues 2-1104 of SEQ ID NO: 8; c) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a mouse TRPM8 protein; d) a polynucleotide that encodes a human TRPM8 protein comprising amino acid residues 1-1268 of SEQ ID NO 11; e) a polynucleotide that encodes a human TRPM8 protein comprising amino acid residues 2-1268 of SEQ ID NO 11; f) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a human TRPM8 protein; and g) a polynucleotide that is complementary to a polynucleotide of a) through f). In some embodiments, the nucleic acid molecule is a) or b) and comprises a first polynucleotide that is 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 9 (mouse TRPM8), or is d) or e) and comprises a first polynucleotide 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 12 (human TRPM8). The nucleic acids can be 90% or more, or 95% or more, identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 9 or SEQ ID NO: 12, or can be identical to the respective polynucleotide. Examples of TRPM8 nucleic acids of the invention include polynucleotides that are 80% or more, 90% or more, or 95% or more, identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 448-3762 of SEQ ID NO: 7 (mouse TRPM8) or nucleotides 61-4821 of SEQ ID NO: 10 (human TRPM8).

[0025] The invention also provides isolated TRPM8 nucleic acid molecules that encode polypeptides that include one or more functional domains of a mammalian (e.g., human or mouse) TRPM8 polypeptide. The polypeptides encoded by these nucleic acid molecules can include, for example, one or more functional domains such as transmembrane regions, pore loop regions, and coiled-coil domains. As an example, the polypeptides can include a pore loop region flanked by two transmembrane regions.

[0026] The invention also provides isolated and/or purified TRPM8 polypeptides. The TRPM8 polypeptides include, for example, a) a mouse TRPM8 protein comprising amino acid residues 1-1104 of SEQ ID NO: 8; b) a mouse TRPM8 protein comprising amino acid residues 2-1104 of SEQ ID NO: 8; c) one or more functional domains of a mouse TRPM8 protein; d) a human TRPM8 protein comprising amino acid residues 1-1268 of SEQ ID NO 11; e) a human TRPM8 protein comprising amino acid residues 2-1268 of SEQ ID NO 11; and f) one or more functional domains of a human TRPM8 protein. For example, the

TRPM8 polypeptides can include one or more functional domains selected from the group consisting of a transmembrane region, a pore loop region, and a coiled-coil domain. In some embodiments, the TRPM8 polypeptides of the invention include a pore loop region flanked by two transmembrane regions.

5 [0027] Methods for identifying an agent that modulates TRPM8-mediated cation passage through a membrane are also provided by the invention. These methods involve: a) providing a membrane that comprises a TRPM8 polypeptide; b) contacting the membrane with a candidate agent; and c) determining whether passage of one or more cations through the membrane is increased in the presence of the candidate agent compared to passage in the
10 absence of the candidate agent. In some embodiments, the membrane is a cell membrane and cation passage through the membrane is detected by measuring cation influx or efflux across the membrane into or out of the cell. To identify antagonists that reduce TRPM8-mediated cation passage, the assay typically is conducted under conditions in which TRPM8 allows cation passage in the absence of the antagonist; e.g., at a temperature of about 20°C or less,
15 or in the presence of menthol. Also provided are methods in which a candidate agent that reduces cation passage is further tested for ability to treat pain by administering the candidate agent to a test animal and determining whether the candidate agent decreases the test animal's response to a pain stimulus. A pain stimulus can include, for example exposure to a temperature below 20°C.

20 [0028] In other embodiments, the invention provides methods for identifying an agent that stimulates TRPM8-mediated cation passage through a membrane. These screens for identifying TRPM8 agonists generally are conducted under conditions in which the TRPM8 polypeptides do not mediate cation passage. Such conditions include, for example, temperatures above about 20°C. Agonists of TRPM8-mediated cation passage are useful as
25 flavor enhancers, fragrances, and the like.

 [0029] The invention also provides methods of reducing pain associated with TRPM8 activity. These methods involve administering to a subject suffering from pain an analgesically effective amount of a compound that reduces TRPM8-mediated cation passage through a membrane or reduces signal transduction from a TRPM8 polypeptide to a DRG
30 neuron. These methods are useful for treating pain that results from, for example, cold exposure, inflammation, tissue damage, and the like. The compounds can be, for example, a) an antibody that specifically binds to a TRPM8 polypeptide; b) an antisense polynucleotide,

ribozyme, or an interfering RNA that reduces expression of a TRPM8 polypeptide; or c) a chemical compound that reduces cation passage through a membrane that comprises a TRPM8 polypeptide.

[0030] Methods for determining whether pain in a subject is mediated by TRPM8 are also provided by the invention. These methods involve obtaining a sample from a region of the subject at which the pain is felt; and testing the sample to determine whether a TRPM8 polypeptide or TRPM8 polynucleotide is present and/or active in the sample. In some embodiments, the presence of a TRPM8 polypeptide in the sample is detected by determining whether cation passage across membranes of cells in the sample is mediated by a TRPM8 polypeptide. TRPM8 involvement in mediating cation passage across membranes of the cells can be determined, for example, by detecting an increase or decrease in cation passage across membranes of the cells when assayed below 20°C and/or in the presence of menthol, compared to cation passage when assayed above 20°C and/or in the absence of menthol. Alternatively, or additionally, the presence of a TRPM8 polypeptide in the sample is detected by contacting the sample with a reagent that specifically binds to a TRPM8 polypeptide. The presence of a TRPM8 polynucleotide in the sample can be detected by, for example, contacting nucleic acids from the sample with a test polynucleotide that can hybridize to a TRPM8 polynucleotide.

[0031] The invention also provides methods for identifying an agent useful in the modulation of a mammalian sensory response. These methods involve: a) contacting a candidate agent with a test system that comprises a receptor polypeptide selected from the group consisting of TRPM8, TRPV3 and TRPV4; and b) detecting a change in activity of the receptor polypeptide in the presence of the candidate agent as compared to the activity of the receptor polypeptide in the absence of the agent, thereby identifying an agent that modulates receptor activity.

[0032] Also provided by the invention are methods for monitoring the efficacy of a treatment of a subject suffering from pain. These methods involve: a) obtaining, at two or more time points in the course of treatment for pain, a sample from a region of the subject at which the pain is felt; and b) testing the samples to determine whether a reduction is observed in amount or activity of one or more members selected from the group consisting of: a TRPV3 polypeptide, a TRPV3 mRNA, a TRPV4 polypeptide, a TRPV4 mRNA, a TRPM8 polypeptide, and a TRPM8 mRNA. In some embodiments, one of the time points is

prior to or simultaneously with administration of the treatment, and the other time point is after treatment has begun.

[0033] The invention provides assays capable of detecting the expression of one or more of TRPV3, TRPV4 or TRPM8 in human tissue. The assays are selected from the group consisting of: a) an assay comprising contacting a human tissue sample with monoclonal antibodies binding to TRPV3, TRPV4 or TRPM8 and determining whether the monoclonal antibodies bind to polypeptides in the sample; and b) an assay comprising contacting a human tissue sample with an oligonucleotide that is capable of hybridizing to a nucleic acid that encodes TRPV3, TRPV4 or TRPM8.

[0034] Methods of treating pain provided by the invention include methods in which a patient suffering from pain mediated by one or more polypeptides selected from the group consisting of TRPV3, TRPV4 and TRPM8 is identified by measuring expression of the polypeptide in tissue from such patient, and administering to such patient an analgesically effective amount of an agent which inhibits the polypeptide.

[0035] The invention also provides methods for identifying an agent useful in the treatment of pain. These methods involve: a) administering a candidate agent to a mammal suffering from pain; b) in a sample obtained from the mammal, detecting an activity or amount of one or more members selected from the group consisting of: a TRPV3 polypeptide, a TRPV3 mRNA, a TRPV4 polypeptide, a TRPV4 mRNA, a TRPM8 polypeptide, and a TRPM8 mRNA; and c) comparing the amount or activity of the member in the presence of the candidate agent with the amount or activity of the member in a sample obtained from the mammal in the absence of the candidate agent, wherein a decrease in amount or activity of the member in the sample in the presence of the candidate agent relative to the amount or activity in the absence of the candidate agent is indicative of an agent useful in the treatment of pain.

[0036] Also provided are methods for identifying an agent that binds to and/or modulates the activity of an mRNA or polypeptide encoded by a TRPV3, TRPV4, or TRPM8 nucleic acid. These methods involve: a) contacting an isolated cell which expresses a heterologous TRPV3, TRPV4, or TRPM8 nucleic acid encoding a polypeptide with the agent; and b) determining binding and/or modulation of the activity of the mRNA or polypeptide by the agent, to identify agents which bind with and/or modulate the activity of the polypeptide.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] Figures 1A and 1B show differential expression of TRPV3 and TRPV4 genes in the Chung model. Figure 1A: mRNA levels of TRPV3 are increased in a rat model of chronic neuropathic pain. The human cDNA sequence of TRPV3 is used to search the Celera mouse genomic DNA database and two primers are derived from regions that are identical from human and mouse sequences. The primers are used to amplify the rat TRPV3 from total RNA samples from the Chung model (L4 and L5 DRG) and sham-operated animals in a standard reverse-transcriptase polymerase chain reaction (RT-PCR) protocol. The top panel shows the gel image from one RT-PCR experiment and the bottom shows the average fold of regulation of TRPV3 in L4 and L5 DRG neurons from Chung model from three independent experiments. Figure 1B: TRPV4 is up-regulated in a rat model of chronic neuropathic pain. For analysis TRPV4 expression in the Chung model (28- and 50-day), first-strand cDNA equivalent to 30 ng of total RNA is used per reaction and amplified between 32/35 cycles for higher expressing genes and 35/38 cycles for lower-expressing genes. Due to the constraints on the amount of total RNA available, half the volume of the PCR reaction is removed at the lower cycle and the remaining reaction is continued for a further 3 cycles. All the samples are resolved on 4-20% TBE gels and densitometry carried out on the clearest, non-saturated bands.

[0038] Figures 2A-2F show the TRPV3 sequence and genomic localization. Figure 2A: Rooted tree showing protein sequence relationship of different members of the TRPV ion channel family. Figure 2B: Relative position of TRPV1 (VR1) and TRPV3 coding sequences on mouse (11B4) and human (17p13) chromosomes. Figure 2C: Comparison of mouse TRPV3 protein sequence to other TRPVs (excluding C-terminal half containing transmembrane domains). Identical sequences are highlighted in dark gray; conserved residues, in light gray. Predicted coiled-coil and ankyrin domains are marked and correspond to regions for TRPV3 only. The protein alignment is generated using Megalign and Boxshade at <http://biowb.sdsc.edu/CGI/BW.cgi>. The coiled-coil domains are predicted using the program Coils (<http://searchlauncher.bcm.tmc.edu/seq-search/struc-predict.html>). The ankyrin domains are predicted using the PFAM protein search (<http://pfam.wustl.edu/hmmsearch.shtml>). Figure 2D: A schematic of TRPV3 and predicted membrane topology. Figure 2E: Kyte Doolittle hydrophobicity plot of TRPV3 sequences showing the 6 transmembrane domains (1-6) and the pore domain (P). Figure 2F: Coiled-

coil domain prediction of TRPV3 sequence by Coils shows two 14-mer peaks at the N-terminal, prior to ankyrin sequences.

[0039] Figures 3A-3D demonstrate that TRPV3 is activated by heat. Currents evoked by heat in TRPV3 expressing Chinese Hamster Ovary (CHO) cells. Figure 3A:

5 Inward current to temperature ramp, $V_h = -60$ mV, in calcium free external solutions. Figure 3B: Heat evoked currents of the same cell in Ca^{2+} -free and subsequently in Ca^{2+} containing solutions showing increased inward current in Ca^{2+} conditions. Figure 3C: Semi-logarithmic plot of current against temperature with double exponential fitted line for the same trace as Figure 3A. Note the discontinuity at $\sim 32^\circ\text{C}$ (arrow). Figure 3D: Current-voltage relationship
10 in calcium containing external solution showing the pronounced outward rectification of TRPV3 at 48°C but not at room temperature. Note the small outward currents at room temperature.

[0040] Figures 4A-4D. TRPV3 becomes sensitized to repeated applications of the heat stimulus. Figure 4A: Repeated heat steps from 25 - 45°C evoke increased inward current
15 responses. Figure 4B: The outward rectification becomes more pronounced with repeated voltage ramps in 48°C external solution. Both experiments are conducted in the presence of 2 mM CaCl_2 in the external solution. Figure 4C: Control protocol for antagonist experiments. Note that the responses continue to sensitize with repeated heat steps in the absence of putative antagonists. Figure 4D: 1 μM ruthenium red attenuates the sensitization
20 and inhibits the heat response.

[0041] Figure 5. TRP Channels in thermosensation. Four TRP channels implicated in thermosensation cover most but not all physiologically relevant temperatures.

[0042] Figures 6A-6D show results of an analysis of the nucleotide and amino acid sequences of TRPM8. Figure 6A: Comparison of mouse TRPM8 protein sequence to
25 some of its closest relatives, TRPM1 (human Melastatin, GI 6006023), TRPM2 (human, GI 4507688) and TRPM7 (mouse Chak, GI 14211382). The alignment is generated using Megalign and Boxshade. Identical or conserved residues are shown in white letters on a black background. Figure 6B: Phylogenetic tree showing protein sequence relationship of different members of the TRP ion channel super-family. TRPs are subdivided into three
30 main subfamilies: TRPMs, TRPVs and TRPCs. The TRPMs do not contain any Ankyrin domains in their N-terminal domains. The transmembrane domains have the highest homology among different classes of TRP channels. Figure 6C: Kyte Doolittle

hydrophobicity plot of TRPM8 sequences showing the eight hydrophobic peaks demarking the potential transmembrane regions of the protein that spans from 695-1024 amino acids.

Figure 6D: Coiled-coil domain prediction of TRPM8 sequence by the program coils shows multiple 14-mer peaks at the N- and C-terminus of the transmembrane spanning domains

5 (<http://searchlauncher.bcm.tmc.edu/seq-search/struc-predict.html>).

[0043] Figures 7A-7E: Increase in intracellular calcium concentration ($[Ca^{2+}]_i$) in TRPM8-expressing CHO cells in response to cold and menthol. Figure 7A: mTRPM8 CHO cells show a rapid increase in $[Ca^{2+}]_i$ when the temperature reaches $\sim 15^\circ C$. Non-transfected CHO cells do not show a response to cold. Removal of external Ca^{2+} completely abolishes the response to cooling. Figure 7B: The estimated average threshold temperature at which $[Ca^{2+}]_i$ begins to increase is approximately $23^\circ C$ for mTRPM8. TRPM8-expressing CHO cells are cooled from $33-23^\circ C$, upon which an increase in Ca^{2+} is observed. Continuous cooling of the cells to $20^\circ C$ shows a marked Ca^{2+} increase followed by a rapid return to near-basal levels upon warming to $33^\circ C$. Figure 7C: TRPM8 responses, evoked by repeated applications of a $23^\circ C$ temperature stimulus show little desensitization in calcium-containing standard bath solution. Figure 7D: TRPM8 responds to menthol at $25^\circ C$. Intensity of the TRPM8 response is dependent on menthol concentrations. A 10-fold increase in menthol concentration results in a larger influx of Ca^{2+} . This response is suppressed in the absence of extracellular Ca^{2+} . Non-transfected CHO cells exhibit no increase in $[Ca^{2+}]_i$ upon application of menthol. Figure 7E: At $33^\circ C$, $10 \mu M$ menthol does not elicit an influx of Ca^{2+} . When the temperature of the bath solution is lowered to $30^\circ C$, a marked increase in intracellular Ca^{2+} is observed. Additionally, repeated applications of menthol do not appear to desensitize TRPM8-expressing cells. These experiments suggest that menthol simulates the effect of cooling in TRPM8-expressing cells. This identification of a cold-sensing TRP channel involved in thermoreception reveals an expanded role for this family in somatic sensory detection.

10
15
20
25

[0044] Figures 8A-8B show an increase in intracellular calcium concentration $[Ca^{2+}]_i$ in TRPM8-expressing CHO cells in response to cold. Figure 8A: TRPM8-transfected CHO cells show a rapid increase in $[Ca^{2+}]_i$ when the temperature is lowered from $25^\circ C$ to $15^\circ C$. The stimulus period is indicated below the traces. Non-transfected CHO cells do not show a response to cold. Removal of external Ca^{2+} completely suppresses the response to cooling. Experiments are performed in triplicate. The average response (\pm SEM) of 20-30

30

cells from a representative experiment is presented. Figure 8B: Increase in $[Ca^{2+}]_i$ due to decrease in temperature from 35°C to 13°C in TRPM8⁺ cells. The panel shows mean \pm SEM for 34 individual cells. Note the increase starts to occur between 22°C and 25°C.

[0045] Figures 9A-9B show that current is evoked by reduction in temperature in TRPM8-expressing CHO cells. Figure 9A: Outward currents evoked at +60 mV by reducing the temperature from 35°C to 10°C. In this cell the current activates at 19.3°C as indicated in the right hand panel. Figure 9B: Current-voltage relationship for currents activated at 20.5°C and 33.5°C. Increasing the temperature reduces the amplitude of outward currents.

[0046] Figures 10A-10B show that current is evoked by menthol in TRPM8-expressing CHO cells. Figure 10A: Inward currents evoked by 1 mM menthol ($V_h = -60$ mV) are inactivated by increasing the temperature from 25°C to 45°C. Figure 10B: Current-voltage relationship for response to 1 mM menthol. Currents show pronounced outward-rectification in the presence of menthol not seen in the absence of this agonist.

[0047] Figures 11A-11B show a dose-response curve for menthol-stimulated current in TRPM8-expressing CHO cells. The voltage employed was +60 mV. Figure 11A: Single examples, from two different cells, of current evoked by applying 0.1, 0.5, 1 and 10 mM menthol at 22°C and 35°C. Figure 11B: Comparison of response (mean \pm SEM, $n=5$ for all points) of current evoked by menthol either at 22°C or 35°C.

DESCRIPTION OF THE SEQUENCE LISTING

[0048] SEQ ID NO: 1 provides a nucleotide sequence that encodes a mouse TRPV3 polypeptide, and upstream and downstream regions. The open-reading frame extends from nucleotides 65-2440.

[0049] SEQ ID NO: 2 provides an amino acid sequence of a mouse TRPV3 polypeptide.

[0050] SEQ ID NO: 3 provides nucleotide sequences for all polynucleotides that code for the mouse TRPV3 amino acid sequence presented in SEQ ID NO: 2.

[0051] SEQ ID NO: 4 provides a nucleotide sequence that encodes a human TRPV3 polypeptide, and an upstream non-coding region. The open-reading frame extends from nucleotides 57-2432.

[0052] SEQ ID NO: 5 provides an amino acid sequence of a human TRPV3 polypeptide.

[0053] SEQ ID NO: 6 provides nucleotide sequences for all polynucleotides that code for the human TRPV3 amino acid sequence presented in SEQ ID NO: 5.

[0054] SEQ ID NO: 7 provides a nucleotide sequence that encodes a mouse TRPM8 polypeptide, and upstream and downstream non-coding regions. The coding region
5 extends from nucleotides 448-3762.

[0055] SEQ ID NO: 8 provides an amino acid sequence of a mouse TRPM8 polypeptide.

[0056] SEQ ID NO: 9 provides nucleotide sequences for all polynucleotides that code for the mouse TRPM8 amino acid sequence presented in SEQ ID NO: 8.

10 [0057] SEQ ID NO: 10 provides a nucleotide sequence that encodes a human TRPM8 polypeptide, and upstream and downstream non-coding regions. The coding region extends from nucleotides 61-4821.

[0058] SEQ ID NO: 11 provides an amino acid sequence of a human TRPM8 polypeptide.

15 [0059] SEQ ID NO: 12 provides nucleotide sequences for all polynucleotides that code for the human TRPM8 amino acid sequence presented in SEQ ID NO: 11.

[0060] SEQ ID NO: 13 provides a nucleotide sequence that encodes a mouse TRPV4 polypeptide, and upstream and downstream regions. The open-reading frame extends from nucleotides 156-2771.

20 [0061] SEQ ID NO: 14 provides an amino acid sequence of a mouse TRPV4 polypeptide.

[0062] SEQ ID NO: 15 provides nucleotide sequences for all polynucleotides that code for the mouse TRPV4 amino acid sequence presented in SEQ ID NO: 14.

[0063] SEQ ID NO: 16 provides a nucleotide sequence that encodes a human
25 TRPV4 polypeptide.

[0064] SEQ ID NO: 17 provides an amino acid sequence of a human TRPV4 polypeptide.

[0065] SEQ ID NO: 18 provides nucleotide sequences for all polynucleotides that code for the human TRPV4 amino acid sequence presented in SEQ ID NO: 17.

DETAILED DESCRIPTION

Definitions

[0066] A "host cell," as used herein, refers to a prokaryotic or eukaryotic cell that contains heterologous DNA that has been introduced into the cell by any means, e.g.,
5 electroporation, calcium phosphate precipitation, microinjection, transformation, viral infection and the like.

[0067] "Heterologous" as used herein means "of different natural origin" or represent a non-natural state. For example, if a host cell is transformed with a DNA or gene derived from another organism, particularly from another species, that gene is heterologous
10 with respect to that host cell and also with respect to descendants of the host cell which carry that gene. Similarly, heterologous refers to a nucleotide sequence derived from and inserted into the same natural, original cell type, but which is present in a non-natural state, e.g., a different copy number, or under the control of different regulatory elements.

[0068] A "vector" molecule is a nucleic acid molecule into which heterologous
15 nucleic acid may be inserted which can then be introduced into an appropriate host cell. Vectors preferably have one or more origins of replication, and one or more sites into which the recombinant DNA can be inserted. Vectors often have convenient means by which cells with vectors can be selected from those without, e.g., they encode drug resistance genes. Common vectors include plasmids, viral genomes, and (primarily in yeast and bacteria)
20 "artificial chromosomes".

[0069] "Plasmids" generally are designated herein by a lower case p preceded and/or followed by capital letters and/or numbers, in accordance with standard naming conventions that are familiar to those of skill in the art. Starting plasmids disclosed herein are either commercially available, publicly available on an unrestricted basis, or can be
25 constructed from available plasmids by routine application of well-known, published procedures. Many plasmids and other cloning and expression vectors that can be used in accordance with the present invention are well-known and readily available to those of skill in the art. Moreover, those of skill readily may construct any number of other plasmids suitable for use in the invention. The properties, construction and use of such plasmids, as
30 well as other vectors, in the present invention will be readily apparent to those of skill from the present disclosure.

[0070] The terms “nucleic acid”, “DNA sequence” or “polynucleotide” refer to a deoxyribonucleotide or ribonucleotide polymer in either single- or double-stranded form, and unless otherwise limited, encompasses known analogues of natural nucleotides that hybridize to nucleic acids in manner similar to naturally-occurring nucleotides. Although
5 polynucleotide sequences presented herein recite “T” (for thymidine), which is found only in DNA, the sequences also encompass the corresponding RNA molecules in which each “T” in the DNA sequence is replaced by “U” for uridine.

[0071] The term “isolated” refers to material that is substantially or essentially free from components which normally accompany the material as found in its native state.
10 Thus, the polypeptides and nucleic acids of the invention do not include materials normally associated with their *in situ* environment. An isolated nucleic acid, for example, is not associated with all or part of the chromosomal DNA that would otherwise flank the nucleic acid. Typically, isolated proteins of the invention are at least about 80% pure, usually at least about 90%, and preferably at least about 95% pure as measured by band intensity on a
15 silver stained gel or other method for determining purity. Protein purity or homogeneity can be indicated by a number of means well-known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualization upon staining. For certain purposes high resolution will be needed and HPLC or a similar means for purification utilized.

20 [0072] The terms “identical” or percent “identity”, in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms or by visual inspection.

25 [0073] The phrase “substantially identical”, in the context of two nucleic acids or polypeptides, refers to two or more sequences or subsequences that have at least 70%, preferably 80%, most preferably 90-95% nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms or by visual inspection. Preferably, the substantial identity
30 exists over a region of the sequences that is at least about 50 residues in length, more preferably over a region of at least about 100 residues, and most preferably the sequences are

substantially identical over at least about 150 residues. In a most preferred embodiment, the sequences are substantially identical over the entire length of the coding regions.

[0074] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison
5 algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[0075] Optimal alignment of sequences for comparison can be conducted, e.g., by
10 the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.*, 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.*, 48:443 (1970), by the search for similarity method of Pearson & Lipman, *Proc. Natl. Acad. Sci. USA*, 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group,
15 575 Science Drive, Madison, WI), or by visual inspection (see generally, *Current Protocols in Molecular Biology*, F.M. Ausubel et al., eds., Current Protocols, a joint venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc., (1995 Supplement) (Ausubel)).

[0076] Examples of algorithms that are suitable for determining percent sequence
20 identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., *J. Mol. Biol.*, 215:403-410 (1990) and Altschuel et al., *Nucleic Acids Res.*, 25:3389-3402 (1997), respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high-scoring
25 sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al., *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in
30 both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for

mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more
5 negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters wordlength (W), T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a W of 11, an expectation (E) of 10, $M=5$, $N=-4$, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a W of 3, an E of 10 and the BLOSUM62
10 scoring matrix (see Henikoff & Henikoff, *Proc. Natl. Acad. Sci. USA*, 89:10915 (1989)). Percent identities, where specified herein, are typically calculated using the Blast 2.0 implementation using the default parameters.

[0077] In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin
15 & Altschul, *Proc. Natl. Acad. Sci. USA*, 90:5873-5787 (1993)). One measure of similarity provided by the BLAST algorithm is the smallest sum probability ($P(N)$), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to
20 the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

[0078] Another indication that two polynucleotides are substantially identical is that the polynucleotides hybridize to each other under specified hybridization conditions. Examples of stringent hybridization conditions include: incubation temperatures of about
25 25°C to about 37°C; hybridization buffer concentrations of about 6 x SSC to about 10 x SSC; formamide concentrations of about 0% to about 25%; and wash solutions of about 6 x SSC. Examples of moderate hybridization conditions include: incubation temperatures of about 40°C to about 50°C; buffer concentrations of about 9 x SSC to about 2 x SSC; formamide concentrations of about 30% to about 50%; and wash solutions of about 5 x SSC
30 to about 2 x SSC. Examples of high stringency conditions include: incubation temperatures of about 55°C to about 68°C; buffer concentrations of about 1 x SSC to about 0.1 x SSC; formamide concentrations of about 55% to about 75%; and wash solutions of about 1 x SSC,

0.1 x SSC or deionized water. In general, hybridization incubation times are from 5 minutes to 24 hours, with 1, 2 or more washing steps, and wash incubation times are about 1, 2 or 15 minutes. SSC is 0.15 M NaCl and 15 mM citrate buffer. It is understood that equivalents of SSC using other buffer systems can be employed.

5 [0079] A further indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross-reactive with the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions.

10 Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions, as described below.

 [0080] "Conservatively modified variations" of a particular polynucleotide sequence refers to those polynucleotides that encode identical or essentially identical amino acid sequences, or where the polynucleotide does not encode an amino acid sequence, to

15 essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given polypeptide. For instance, the codons CGU, CGC, CGA, CGG, AGA and AGG all encode the amino acid arginine. Thus, at every position where an arginine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such

20 nucleic acid variations are "silent variations," which are one species of "conservatively modified variations". Every polynucleotide sequence described herein which encodes a polypeptide also describes every possible silent variation, except where otherwise noted. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine) can be modified to yield a functionally identical

25 molecule by standard techniques. Accordingly, each "silent variation" of a nucleic acid which encodes a polypeptide is implicit in each described sequence.

 [0081] Furthermore, one of skill will recognize that individual substitutions, deletions or additions which alter, add or delete a single amino acid or a small percentage of amino acids (typically less than 5%, more typically less than 1%) in an encoded sequence are

30 "conservatively modified variations" where the alterations result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art (see, e.g., Creighton, *Proteins*,

W.H. Freeman and Company (1984)). Individual substitutions, deletions or additions which alter, add or delete a single amino acid or a small percentage of amino acids in an encoded sequence are also “conservatively modified variations”.

5 [0082] The term “recombinant” when used with reference to a cell, or nucleic acid, or vector, indicates that the cell, or nucleic acid, or vector, has been modified by the introduction of a heterologous nucleic acid or the alteration of a native nucleic acid, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells can contain genes that are not found within the native (non-recombinant) form of the cell or can express native genes that are otherwise abnormally expressed, under expressed or not expressed at
10 all. Recombinant cells can also contain genes found in the native form of the cell wherein the genes are modified and re-introduced into the cell by artificial means. The term also encompasses cells that contain a nucleic acid endogenous to the cell that has been modified without removing the nucleic acid from the cell; such modifications include those obtained by gene replacement, site-specific mutation and related techniques.

15 [0083] The term “modulate” refers to a change in the activity and/or amount of TRPV3, TRPV4 or TRPM8 proteins. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional or immunological properties of such proteins. The term “modulation” also refers to a change in the increase or decrease in the level of expression of mRNA or protein encoded by the
20 TRPV3, TRPV4, and TRPM8 genes.

 [0084] The term “operably-linked”, as used herein, refer to functionally-related nucleic acid sequences. A promoter is operably associated or operably-linked with a coding sequence if the promoter controls the translation of the encoded polypeptide. While operably-linked nucleic acid sequences can be contiguous and in the same reading frame,
25 certain genetic elements, e.g., repressor genes, are not contiguously linked to the sequence encoding the polypeptide but still bind to operator sequences that control expression of the polypeptide.

 [0085] The term “agonist”, as used herein, refers to a molecule which, when bound to the TRPV3, TRPV4 and TRPM8 proteins, increases or prolongs the duration of the
30 effect of the biological or immunological activity of such proteins. Agonists may include proteins, nucleic acids, carbohydrates or any other molecules which bind to and modulate the effect of these proteins.

[0086] The term “antagonist”, as used herein, refers to a molecule which, when bound to TRPV3, TRPV4 and TRPM8 proteins, decreases the amount or the duration of the effect of the biological or immunological activity of these proteins. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies or any other molecules which decrease the effect of these proteins. The term “antagonist” can also refer to a molecule which decreases the level of expression of mRNA and/or translation of protein encoded by TRPV3, TRPV4, and TRPM8 genes. Examples of such antagonists include antisense polynucleotides, ribozymes and double-stranded RNAs.

[0087] In practicing the present invention, many conventional techniques in molecular biology, microbiology and recombinant DNA are used. These techniques are well-known and are explained in, e.g., *Current Protocols in Molecular Biology*, Vols. I, II and III, F.M. Ausubel, ed. (1997); Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 3rd Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (2001); *DNA Cloning: A Practical Approach*, Vols. I and II, D.N. Glover, ed. (1985); *Oligonucleotide Synthesis*, M.L. Gait, ed. (1984); *Nucleic Acid Hybridization*, Hames and Higgins (1985); *Transcription and Translation*, Hames and Higgins, eds. (1984); *Animal Cell Culture*, R.I. Freshney, ed. (1986); *Immobilized Cells and Enzymes*, IRL Press (1986); Perbal, *A Practical Guide to Molecular Cloning*; the series, *Methods in Enzymology*, Academic Press, Inc. (1984); *Gene Transfer Vectors for Mammalian Cells*, J.H. Miller and M.P. Calos, eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (1987); and *Methods in Enzymology*, Vols. 154 and 155, Wu and Grossman, and Wu, eds., respectively.

Description of the Preferred Embodiments

[0088] The present invention relates to novel nucleic acids known as TRPV3 (previously known as VRLX, VRL-S, VR4 and TRPV7), TRPV4 (previously known as VRL3 and OTRPC4), and TRPM8 (previously known as TRPX) that are homologous to the VR1, polypeptides encoded by these nucleic acids, recombinant materials and methods for their production. The specific names given to the three genes follow the nomenclature suggested in Montell et al., *Molecular Cell*, 9:229-231 (2002). The genes have been found to be expressed either in keratinocytes or the DRG, and both TRPV3 and TRPM8 proteins function in temperature sensation. In addition, expression of the TRPV3 and TRPV4 genes

is up-regulated in a rat injury model (see Examples 4 and 6). The present invention also relates to the identification of trkA^+ pain-specific genes that are expressed in the DRG. Since the aforementioned genes are expressed in keratinocytes and the DRG, function in temperature sensation, and are up-regulated in response to injury, these genes and their related polypeptides can serve as specific therapeutic targets for the design of drugs to treat chronic and nociceptive pain, inflammation and skin disorders. Accordingly, the invention also relates to methods for identifying agents useful in treating pain, inflammation and skin disorders, methods for treating pain, inflammation and skin disorders and methods of monitoring the efficacy of a treatment, utilizing these genes and polypeptides. These genes and related polypeptides can also be utilized in diagnostic methods for the detection of pain, inflammation and skin disorders.

[0089] TRPV3, TRPV4 and TRPM8 belong to the VR family. A Hidden Markov Model (HMM) of the VR1 and VRL1 proteins from different mammalian species including human and an HMM model against Transmembrane 6 (TM6) domain of all known TRP/VRs has been constructed. The six-frame translation of the Human Celera database has been searched against the VR model. Multiple new putative exons with high homology (70% identical and 82% similar in conserved regions among the different VR/TRPs) to Transmembrane 4 (TM4) and TM6 domains to the known TRPs have been identified. These exons map to bacterial artificial chromosomes containing specific human sequences from the High Throughput Genome Sequence (HTGS) database. All the newly-identified exons belong to three new genes of the VR family. Subsequently, RT-PCR has confirmed that these genes are expressed in the DRG or keratinocytes. The structural homology to known TRP channels, the genes' expression in DRG or keratinocytes, their function as temperature-sensitive channels, and the up-regulation of TRPV3 and TRPV4 gene expression observed in a rat injury model in the DRG, indicate that the new genes act as important sensory receptors.

TRPV3: An Ion Channel Responsive to Warm and Hot Temperatures

[0090] TRPV3 is the first molecule described to be activated at warm and hot temperatures, and to be expressed in skin cells (see Examples 2 and 3). TRPV3 signaling mediates a cell-autonomous response in keratinocytes upon exposure to heat. The heat-induced TRPV3 signal is transferred to nearby free nerve endings, thereby contributing to

conscious sensations of warm and hot. This is supported by indirect evidence that skin cells can act as thermal receptors. For instance, while dissociated DRG neurons can be directly activated by heat and cold, warm receptors have only been demonstrated in experiments where skin-nerve connectivity is intact (see Hensel et al., *Pfugers Arch.*, 329:1-8 (1971), Hensel et al., *J. Physio.*, 204:99-112 (1969)). TRPV3 has an activation threshold around 33-35°C. The presence of such a warm receptor in skin (with a resting temperature of 34°C) and not DRG neurons (with a resting temperature of 37°C at the cell body) prevents a warm-channel like TRPV3 from being constitutively active at core 37°C temperatures. The residual heat sensitivity in TRPV1 knockout mice also involves skin cells: while dissociated DRG neurons from TRPV1-null animals do not respond to moderate noxious stimulus at all, skin-nerve preparations from such animals do respond (see Caterina et al., *Science*, 288:306-13 (2000); Davis et al., *Nature*, 405:183-187 (2000); Roza et al., Paper presented at the 31st Annual meeting for the Society of Neuroscience, San Diego, CA (2001)). Collectively these data indicate that a warm/heat receptor is present in the skin, in addition to the heat receptors in DRGs. While synapses have not been found between keratinocytes and sensory termini; ultrastructural studies have shown that keratinocytes contact, and often surround, DRG nerve fibers through membrane-membrane apposition (see Hilliges et al., *J. Invest. Dermatol.*, 104:134-137 (1995) and Cauna., *J. Anat.*, 115:277-288 (1973)). Therefore, heat-activated TRPV3 signal from keratinocytes can be transduced to DRG neurons through direct chemical signaling. One potential signaling mechanism can involve ATP. P2X3, an ATP-gated channel, is present in sensory endings, and analysis of P2X3 knockout mice show a strong deficit in coding of warm temperatures (see Souslova et al., *Nature*, 407:1015-1017 (2000); Cockayne et al., *Nature*, 407:1011-1015 (2000)). Furthermore, release of ATP from damaged keratinocytes has been shown to cause action potentials in nociceptors via the P2X receptors (see Cook et al., *Pain*, 95:41-47 (2002)). Since TRPV3 is activated at innocuous warm and noxious hot temperatures and is expressed in skin, this gene can serve as a therapeutic target for the design of drugs useful in treating pain, inflammation and skin disorders, e.g., those associated with sunburn and other sensitized states.

[0091] In one aspect, the invention provides isolated nucleic acids encoding a mammalian TRPV3 protein. These include an isolated and/or recombinant nucleic acid molecule that encodes a mouse TRPV3 protein having an amino acid sequence as shown in SEQ ID NO: 2. For example, the TRPV3-encoding nucleic acids of the invention include

those that have a nucleotide sequence as set forth in SEQ ID NO: 1, from nucleotides 65-2440. The nucleic acids of the invention can include not only the coding region, but also the non-coding regions that are upstream and downstream of the coding region and also are provided in SEQ ID NO: 1. The invention also provides an isolated mouse TRPV3 polypeptide having an amino acid sequence as shown in SEQ ID NO: 2. Also provided are numerous other nucleic acids that encode this mouse TRPV3 polypeptide; the nucleotide sequences of these nucleic acids are shown in SEQ ID NO: 3.

[0092] Human TRPV3 polypeptides and polynucleotides are also provided by the invention. For example, the invention provides an isolated and/or recombinant human TRPV3-encoding polynucleotide encoding a human TRPV3 polypeptide having an amino acid sequence as set forth in SEQ ID NO: 5. These nucleic acid molecules include those that have a nucleotide sequence as set forth in nucleotides 57-2432 of SEQ ID NO: 4. Upstream and downstream non-coding regions are also provided in SEQ ID NO: 4. Also provided by the invention are isolated human TRPV3 polypeptides having an amino acid sequence as set forth in SEQ ID NO: 5. The invention also provides numerous other nucleic acids that encode this human TRPV3 polypeptide; the nucleotide sequences of these nucleic acids are shown in SEQ ID NO: 6.

TRPV4: An Ion Channel that is Activated by Pain

[0093] TRPV4 is a TRP channel protein that is expressed in adult mouse kidney, newborn dorsal root ganglion and adult trigeminal tissue (see Example 5). TRPV4 is a nonselective cation channel that is activated by decreases in, and is inhibited by increases in, extracellular osmolarity indicating that this channel functions as an osmosensor channel (see, e.g., Strotmann et al., *Nat. Cell Biol.*, 2:695-702 (2000)). In addition, expression of the TRPV4 gene is up-regulated in a rat injury model (see Example 6). Accordingly, the TRPV4 gene can serve as a therapeutic target for the design of drugs to treat pain, kidney disorders and migraine.

[0094] The invention provides isolated nucleic acids that encode a mammalian TRPV4 protein. These include the isolated and/or recombinant nucleic acid molecule that encodes mouse TRPV4 protein having an amino acid sequence as set forth in SEQ ID NO: 14. Included among these nucleic acid molecules are those that have a nucleotide sequence as set forth in nucleotides 156-2771 of SEQ ID NO: 13. Upstream and downstream non-

coding sequences are also provided. Also provided by the invention are isolated mouse TRPV4 polypeptides having an amino acid sequence as set forth in SEQ ID NO: 14. Numerous other nucleic acids that encode this mouse TRPV4 polypeptide are also provided by the invention. The nucleotide sequences of such nucleic acids are shown in SEQ ID NO: 15.

[0095] The mammalian TRPV4-encoding nucleic acids also include the isolated and/or recombinant nucleic acid molecules that encode human TRPV4 protein that has an amino acid sequence as set forth in SEQ ID NO: 17. Such nucleic acid molecules include those having a nucleotide sequence as set forth in SEQ ID NO: 16. Also provided are isolated human TRPV4 polypeptides having an amino acid sequence as set forth in SEQ ID NO: 17. The invention also provides numerous other nucleic acids that encode this human TRPV4 polypeptide; the nucleotide sequences of these nucleic acids are shown in SEQ ID NO: 18.

TRPM8: An Ion Channel Responsive to Cold Temperatures and to Menthol

[0096] TRPM8 is activated by cold stimuli and a cooling agent (menthol) and is expressed in a select group of DRG neurons that share characteristics of thermoreceptive neurons (see Examples 8 and 9).

[0097] Cells over-expressing TRPM8 show increased intracellular calcium levels when subjected to cold temperatures ranging from 23°C to 10°C (the lower limit of our temperature-controlled perfusion system). The calcium influx and electrophysiological studies described below demonstrate that TRPM8 is a non-selective, plasma membrane cation channel activated by cold temperatures. The ionic permeability of TRPM8 is similar to that of other TRP channels, which are permeable to both monovalent and divalent cations, although calcium permeability estimates (P_{Ca}/P_{Na}) vary from 0.3 to 14 (see, e.g., Harteneck et al., *Trends Neurosci.*, 23:159-166 (2000)). Menthol is a cooling compound that likely acts on endogenous cold-sensitive channel(s) (see Schafer et al., *J. Gen. Physiol.*, 88:757-776 (1986)). That TRPM8-expressing cells are activated and modulated by menthol reinforces the idea that TRPM8 indeed functions as a cold-sensitive channel *in vivo*. The finding that the sensitivity to menthol is dependent on temperature is consistent with the behavior of a subset of isolated DRG neurons that show a raised 'cold' threshold in the presence of menthol (see Reid and Flonta, *Nature*, 413:480 (2001)). With respect to the mechanism of

TRPM8 activation, TRPM8 could be directly gated by cold stimulus through a conformational change, or cold temperatures could act through a second messenger system that in turn activates TRPM8. The rapid activation by menthol suggests a direct gating mechanism, at least for this mode of activation.

5 [0098] The expression pattern observed for TRPM8 is consistent with a role in cold thermoception. First, TRPM8 mRNA is highly-specific to DRG neurons. Within the DRG, TRPM8 is expressed in the small-diameter non-myelinated neurons, which correspond to the c-fiber thermoreceptor and nociceptors (see Scott, *Sensory Neurons: Diversity, Development and Plasticity*, Oxford University Press, NY (1992)). The lack of TRPM8
10 expression in *trkA* knockout mice, whose DRGs lack all thermoreceptor and nociceptive neurons, corroborates this finding. Furthermore, the lack of co-expression with VR1, CGRP or IB4 in the adult suggests that TRPM8 is expressed in a unique population of DRG neurons distinct from well-characterized heat nociceptors. Both soma size of neurons that express VRL1 (medium-large neurons) and their co-expression with NF200 (80%
15 co-expression (see Caterina et al., *Nature*, 398:436-441(1999)) strongly argues that cells expressing TRPM8 and VRL1 are also distinct. Therefore, by using various markers it is shown below that TRPM8 is expressed in a sub-class of nociceptors/thermoreceptors that is distinct from noxious heat sensing neurons, and this correlates well with physiological studies of cold-sensitive DRG neurons (see Hensel, *Thermoreception and Temperature
20 Regulation*, Academic Press, London (1981)). A human gene with a high degree of similarity to mouse TRPM8 but no known function was recently shown to be expressed in prostate tissue (see Tsavaler et al., *Cancer Res.*, 61:3760-3769 (2001)).

 [0099] As the first molecule to respond to cold temperatures and menthol, TRPM8 offers interesting insight into the fundamental biology of cold perception. Modulation of
25 TRPM8 activity is also relevant for therapeutic applications: cold treatment is often used as a method of pain relief, and in some instances, hypersensitivity to cold can lead to cold allodynia in patients suffering from neuropathic pain. Modulation of TRPM8 activity is also relevant for treating acute pain, e.g., toothache and other trigeminal focused pain; and for treating cancer, particularly prostate cancer and other prostate disorders.

30 [0100] The invention provides isolated nucleic acids encoding a TRPM8 mammalian protein. These include the isolated and/or recombinant nucleic acid molecules that encode mouse TRPM8 protein that have an amino acid sequence as set forth in SEQ ID

NO: 8. For example, the invention provides recombinant and/or isolated nucleic acid molecules that have a nucleotide sequence as set forth in nucleotides 448-3762 of SEQ ID

NO: 7. Upstream and downstream non-coding regions are also provided. The invention also provides isolated mouse TRPM8 polypeptides that include an amino acid sequence as set
5 forth in SEQ ID NO: 8. Also provided are numerous other nucleic acids that encode this mouse TRPM8 polypeptide. Nucleotide sequences of these nucleic acids are provided in SEQ ID NO: 9.

[0101] The nucleic acids encoding a mammalian TRPM8 protein also include isolated and/or recombinant nucleic acid molecules that encode a human TRPM8 protein
10 comprising an amino acid sequence as set forth in SEQ ID NO: 11. For example, the invention provides an isolated and/or recombinant nucleic acid molecule that includes a nucleotide sequence as set forth from nucleotides 61-4821 of SEQ ID NO: 10. Upstream and downstream non-coding regions are also provided by the invention. The invention also provides isolated human TRPM8 polypeptides having an amino acid sequence as set forth in
15 SEQ ID NO:11. The TRPM8 protein is responsive to cold and menthol.

Nucleic Acid Molecules

[0102] Nucleic acid molecules of the present invention also include isolated nucleic acid molecules that have at least 80% sequence identity, preferably at least 90% identity, preferably at least 95% identity, more preferably at least 98% identity, and most
20 preferably at least 99% identity to a nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 11, SEQ ID NO: 14 or SEQ ID NO: 17, respectively, over the entire coding region or over a subsequence thereof. Such nucleic acid molecules include a nucleic acid having a nucleotide sequence as set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ
25 ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 18, as set forth above.

[0103] Nucleic acids of the present invention include isolated nucleic acid molecules encoding polypeptide variants which comprise the amino acid sequences of
30 SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 11, SEQ ID NO: 14 or SEQ ID NO: 17, respectively. Nucleic acids that are amplified using a primer pair disclosed herein are also encompassed by the present invention.

[0104] Further nucleic acids of the present invention also include fragments of the aforementioned nucleic acid molecules. These oligonucleotide probes are preferably of sufficient length to specifically hybridize only to complementary transcripts of the above identified gene(s) of interest under the desired hybridization conditions (e.g., stringent
5 conditions). As used herein, the term "oligonucleotide" refers to a single-stranded nucleic acid. Generally the oligonucleotide probes will be at least 16-20 nucleotides in length, although in some cases longer probes of at least 20-25 nucleotides will be desirable.

[0105] The oligonucleotide probes can be labeled with one or more labeling moieties to permit detection of the hybridized probe/target polynucleotide complexes.

10 Labeling moieties can include compositions that can be detected by spectroscopic, biochemical, photochemical, bioelectronic, immunochemical, electrical optical or chemical means. Examples of labeling moieties include, but are not limited to, radioisotopes, e.g., ^{32}P , ^{33}P , ^{35}S , chemiluminescent compounds, labeled binding proteins, heavy metal atoms, spectroscopic markers, such as fluorescent markers and dyes, linked enzymes, mass
15 spectrometry tags and magnetic labels.

[0106] Oligonucleotide probe arrays for expression monitoring can be prepared and used according to techniques which are well known to those skilled in the art as described, e.g., in Lockhart et al., *Nature Biotech.*, 14:1675-1680 (1996); McGall et al., *Proc. Natl. Acad. Sci. USA*, 93:13555-13460 (1996); and U.S. Patent No. 6,040,138.

20 [0107] The invention also provides isolated nucleic acid molecules that are complementary to all the above described isolated nucleic acid molecules.

[0108] An isolated nucleic acid encoding one of the above polypeptides including homologs from species other than mouse or human, may be obtained by a method which comprises the steps of screening an appropriate library under stringent conditions with a
25 labeled probe having the sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 18, or a fragment thereof; and isolating full-length cDNA and genomic clones containing the nucleotide sequences. Such hybridization techniques are well-known to a skilled artisan.

30 [0109] Nucleic acid molecules of the present invention may be obtained, using standard cloning and screening techniques, from a cDNA library derived from mRNA in cells of the DRG using the expressed sequence tag (EST) analysis (see Adams et al.,

Science, 252:1651-1656 (1991); Adams et al., *Nature*, 355:632-634 (1992); Adams et al., *Nature*, 377;Suppl. 3:174 (1995)). Polynucleotides of the invention can also be obtained from natural sources such as genomic DNA libraries or can be synthesized using well-known and commercially available techniques.

5 [0110] It is also appreciated by one skilled in the art, that an isolated cDNA sequence can be incomplete, in that the region coding for the polypeptide is short at the 5' end of the DNA. This can occur due to the failure of the reverse transcriptase to complete a DNA copy of the mRNA transcript during the synthesis of the first strand of cDNA. Methods for obtaining full-length cDNAs, or to extend short cDNAs, are well-known in the
10 art, e.g., those based on the method of RACE as described in Frohman et al., *Proc. Natl. Acad. Sci. USA*, 85:8998-9002 (1988). The RACE technique has been modified as exemplified by Marathon™ technology (Clontech Laboratories, Inc.), wherein cDNAs have been prepared from mRNA extracted from a selected tissues and an adaptor sequence is ligated to each end. Subsequently, nucleic acid amplification (PCR) is carried out to amplify
15 the missing 5-end of the cDNA using a combination of gene specific and adaptor specific oligonucleotide primers. The PCR reaction is repeated using primers known as nested primers that are designed to anneal with the amplified product, which is generally an adaptor specific primer that anneals further 3' in the adaptor sequence and a gene specific primer that anneals further 5' in the known gene sequence. The reaction products are then analyzed by
20 DNA sequencing and a full-length cDNA is prepared either by directly joining the product to the existing cDNA to provide a complete sequence, or by carrying out a separate full-length PCR using the new sequence information for the design of the 5' primer.

 [0111] When nucleic acid molecules of the present invention are utilized for the recombinant production of polypeptides of the present invention, the polynucleotide can
25 include the coding sequence for the mature polypeptide, by itself; or the coding sequence for the mature polypeptide in reading frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, pro- or prepro-protein sequence, or other fusion peptide portions. For example, a marker sequence which facilitates purification of the fused polypeptide can be encoded, e.g., a hexa-histidine peptide, as provided in the pQE
30 vector (Qiagen, Inc.) and described in Gentz et al., *Proc. Natl. Acad. Sci. USA*, 86:821-824 (1989), or is an HA tag. The nucleic acid molecule can also contain non-coding 5' and 3'

sequences, such as transcribed, non-translated sequences, splicing and polyadenylation signals, ribosome binding sites and sequences that stabilize mRNA.

Polypeptides and Antibodies

[0112] In another aspect, the present invention relates to mammalian TRPV3, TRPV4 and TRPM8 polypeptides. These include the mouse TRPV3 polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 2, the human TRPV3 polypeptide comprising an amino acid sequence as set forth in SEQ ID: 5, the mouse TRPV4 polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 14, the human TRPV4 polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 17, the mouse TRPM8 polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 8, and the human TRPM8 polypeptide having an amino acid sequence as set forth in SEQ ID NO: 11.

[0113] Further polypeptides of the present invention include isolated polypeptides, i.e., variants, in which the amino acid sequence has at least 90% identity, preferably at least 95% identity, more preferably at least 98% identity and most preferably at least 99% identity, to the amino acid sequences as set forth in SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 11, SEQ ID NO: 14 or SEQ ID NO: 17 over the entire length of these sequences, or a subsequence thereof. Such sequences include the sequences of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 11, SEQ ID NO: 14 and SEQ ID NO: 17.

[0114] The polypeptides of the present invention also include fragments of the aforementioned sequences. For example, the polypeptides of the invention can include amino acids that comprise one or more functional domains of a TRPV3, TRPV4, or TRPM8 polypeptide of the invention. Examples of such domains are described below; other functional domains can be determined using methods known to those of skill in the art.

[0115] The aforementioned TRPV3, TRPV4 and TRPM8 polypeptides can be obtained by a variety of means. Smaller peptides (generally less than 50 amino acids long) may be conveniently synthesized by standard chemical techniques. These polypeptides may also be purified from biological sources by methods well known in the art (see *Protein Purification, Principles and Practice*, 2nd Edition, Scopes, Springer Verlag, NY (1987)). They may also be produced in their naturally occurring, truncated or fusion protein forms by

recombinant DNA technology using techniques well-known in the art. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques and *in vivo* genetic recombination (see, e.g., the techniques described in Sambrook et al., *Molecular Cloning, A Laboratory Manual*, 3rd Edition, Cold Spring Harbor Press, NY (2001); and
5 Ausubel et al., eds., *Short Protocols in Molecular Biology*, 4th Edition, John Wiley & Sons, Inc., NY (1999)). Alternatively, RNA encoding the proteins may be chemically synthesized (see, e.g., the techniques described in *Oligonucleotide Synthesis*, Gait, Ed., IRL Press, Oxford (1984)). Obtaining large quantities of these polypeptides is preferably by recombinant techniques as further described herein.

10 [0116] Accordingly, another aspect of the present invention relates to a method for producing a TRPV3, TRPV4 or TRPM8 polypeptide. These methods generally involve:

a) obtaining a DNA sequence encoding the TRPV3, TRPV4 or TRPM8 polypeptide as defined above; and

b) inserting the DNA into a host cell and expressing the TRPV3, TRPV4 or
15 TRPM8 polypeptide. In some embodiments, the methods further include:

c) isolating the TRPV3, TRPV4 or TRPM8 polypeptide.

[0117] The nucleic acid molecules described herein can be expressed in a suitable host cell to produce active TRPV3, TRPV4 or TRPM8 protein. Expression occurs by placing a nucleotide sequence encoding these proteins into an appropriate expression vector
20 and introducing the expression vector into a suitable host cell, growing the transformed host cell, inducing the expression of one of these proteins, and purifying the recombinant proteins from the host cell to obtain purified, and preferably active, TRPV3, TRPV4 or TRPM8 protein. Appropriate expression vectors are known in the art. For example, pET-14b, pCDNA1Amp and pVL1392 are available from Novagen and Invitrogen and are suitable
25 vectors for expression in *E. Coli*, COS cells and baculovirus infected insect cells, respectively. These vectors are illustrative of those that are known in the art. Suitable host cells can be any cell capable of growth in a suitable media and allowing purification of the expressed TRPV3, TRPV4 or TRPM8 protein. Examples of suitable host cells include bacterial cells, such as *E. Coli*, *Streptococci*, *Staphylococci*, *Streptomyces* and *Bacillus*
30 *subtilis* cells; fungal cells, such as yeast cells, e.g., *Pichia* and *Aspergillus* cells; insect cells, such as *Drosophila* S2 and *Spodoptera* Sf9 cells; mammalian cells, such as CHO, COS, HeLa; and plant cells.

[0118] Growth of the transformed host cells can occur under conditions that are known in the art. The conditions will generally depend upon the host cell and the type of vector used. Suitable induction conditions may be used such as temperature and chemicals and will depend on the type of promoter utilized.

5 [0119] Purification of the TRPV3, TRPV4 or TRPM8 protein can be accomplished using known techniques without performing undue experimentation. Generally, the transformed cells expressing one of these proteins are broken, crude purification occurs to remove debris and some contaminating proteins, followed by chromatography to further purify the protein to the desired level of purity. Cells can be
10 broken by known techniques such as homogenization, sonication, detergent lysis and freeze-thaw techniques. Crude purification can occur using ammonium sulfate precipitation, centrifugation or other known techniques. Suitable chromatography includes anion exchange, cation exchange, high performance liquid chromatography (HPLC), gel filtration, affinity chromatography, hydrophobic interaction chromatography, etc. Well-known
15 techniques for refolding proteins may be used to obtain the active conformation of the protein when the protein is denatured during intracellular synthesis, isolation or purification.

[0120] In another aspect, the present invention relates to antibodies that recognize epitopes within the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 11, SEQ ID NO: 14 or SEQ ID NO: 17. As used herein, the term "antibody"
20 includes, but is not limited to, polyclonal antibodies, monoclonal antibodies, humanized or chimeric antibodies and biologically-functional antibody fragments which are those fragments sufficient for binding of the antibody fragment to the protein. Antibodies specific for proteins encoded by the aforementioned sequences have utilities in several types of applications. These may include, e.g., the production of diagnostic kits for use in detecting
25 and diagnosing pain, particularly in differentiating among different types of pain. Another use would be to link such antibodies to therapeutic agents, such as chemotherapeutic agents, followed by administration to subjects suffering from pain. These and other uses are described in more detail below.

[0121] For the production of antibodies to a protein encoded by one of the
30 disclosed genes, various host animals may be immunized by injection with the polypeptide, or a portion thereof. Such host animals may include but are not limited to rabbits, mice and rats, to name but a few. Various adjuvants may be used to increase the immunological

response, depending on the host species, including but not limited to Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances, such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, dinitrophenol, and potentially useful human adjuvants, such as BCG (*Bacille Calmette-Guerin*) and *Corynebacterium parvum*.

[0122] Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen, such as target gene product, or an antigenic functional derivative thereof. For the production of polyclonal antibodies, host animals, such as those described above, may be immunized by injection with the encoded protein, or a portion thereof, supplemented with adjuvants as also described above.

[0123] Monoclonal antibodies (mAbs), which are homogeneous populations of antibodies to a particular antigen, may be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to the hybridoma technique of Kohler and Milstein, *Nature*, 256:495-497 (1975); and U.S. Patent No. 4,376,110, the human B-cell hybridoma technique (see Kosbor et al., *Immunology Today*, 4:72 (1983); Cole et al., *Proc. Natl. Acad. Sci. USA*, 80:2026-2030 (1983), and the EBV-hybridoma technique (see Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96 (1985)). Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated *in vitro* or *in vivo*. Production of high titers of mAbs *in vivo* makes this the presently preferred method of production.

[0124] In addition, techniques developed for the production of "chimeric antibodies" (see Morrison et al., *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984); Neuberger et al., *Nature*, 312:604-608 (1984); Takeda et al., *Nature*, 314:452-454 (1985)) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable or hypervariable region derived from a murine mAb and a human immunoglobulin constant region.

[0125] Alternatively, techniques described for the production of single chain antibodies (see U.S. Patent No. 4,946,778; Bird, *Science*, 242:423-426 (1988); Huston et al.,

Proc. Natl. Acad. Sci. USA, 85:5879-5883 (1988); and Ward et al., *Nature*, 334:544-546 (1989)) can be adapted to produce differentially expressed gene single-chain antibodies. Single-chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single-chain polypeptide.

5 [0126] Most preferably, techniques useful for the production of "humanized antibodies" can be adapted to produce antibodies to the proteins, fragments or derivatives thereof. Such techniques are disclosed in U.S. Patent Nos. 5,932,448; 5,693,762; 5,693,761; 5,585,089; 5,530,101; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,661,016; and 5,770,429.

10 [0127] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments include but are not limited to: the F(ab')₂ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be constructed (see Huse et al.,
15 *Science*, 246:1275-1281 (1989)) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Assays for Expression of TRPV3, TRPV4 and TRPM8

 [0128] In another aspect, diagnostic assays are provided which are capable of detecting the expression of one or more of TRPV3, TRPV4 or TRPM8 in human tissue.
20 Such assays are particularly useful in identifying subjects suffering from pain and differentiating among different types of pain. As stated above, expression of the TRPV3 and TRPV4 genes are up-regulated in a rat injury model. Accordingly, up-regulation of the TRPV3 and TRPV4 genes in a sample obtained from a subject suffering from pain compared with a normal value of expression of these genes, e.g., a sample obtained from a subject not
25 suffering from pain, or a pre-established control for which expression of the gene was determined at an earlier time, is indicative of a subject suffering from pain. Expression of one or more of these genes can be detected by measuring either protein encoded by the gene or mRNA corresponding to the gene in a tissue sample, particularly from a human tissue sample obtained from a site of pain.

30 [0129] Expression of the TRPV3, TRPV4 and TRPM8 proteins can be detected by a probe which is detectably-labeled, or which can be subsequently-labeled. Generally, the

probe is an antibody which recognizes the expressed protein as described above, especially a monoclonal antibody. Accordingly, in one embodiment, an assay capable of detecting the expression of one or more of TRPV3, TRPV4 or TRPM8 genes comprises contacting a human tissue sample with antibodies preferably monoclonal antibodies, that bind to TRPV3, TRPV4 or TRPM8 polypeptides and determining whether the monoclonal antibodies bind to the polypeptides in the sample.

[0130] Immunoassay methods which utilize the antibodies include, but are not limited to, dot blotting, western blotting, competitive and non-competitive protein binding assays, enzyme-linked immunosorbant assays (ELISA), immunohistochemistry, fluorescence-activated cell sorting (FACS) and others commonly used and widely-described in scientific and patent literature, and many employed commercially.

[0131] Particularly preferred, for ease of detection, is the sandwich ELISA, of which a number of variations exist, all of which are intended to be encompassed by the present invention. For example, in a typical forward assay, unlabeled antibody is immobilized on a solid substrate and the sample to be tested is brought into contact with the bound molecule, followed by incubation for a period of time sufficient to allow formation of an antibody-antigen binary complex. At this point, a second antibody, labeled with a reporter molecule capable of inducing a detectable signal, is then added and incubated, allowing time sufficient for the formation of a ternary complex of antibody-antigen-labeled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by observation of a signal, or may be quantitated by comparing with a control sample containing known amounts of antigen. Variations on the forward assay include the simultaneous assay, in which both sample and antibody are added simultaneously to the bound antibody, or a reverse assay in which the labeled antibody and sample to be tested are first combined, incubated and added to the unlabeled surface bound antibody. These techniques are well-known to those skilled in the art, and the possibility of minor variations will be readily apparent. As used herein, "sandwich assay" is intended to encompass all variations on the basic two-site technique. For the immunoassays of the present invention, the only limiting factor is that the labeled antibody be an antibody which is specific for the protein expressed by the gene of interest, e.g., TRPV3 or a fragment thereof.

[0132] The most commonly used reporter molecules in this type of assay are either enzymes, fluorophore- or radionuclide-containing molecules. In the case of an

enzyme immunoassay an enzyme is conjugated to the second antibody, usually by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different ligation techniques exist, which are well-known to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase and alkaline phosphatase, among others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable color change. For example, p-nitrophenyl phosphate is suitable for use with alkaline phosphatase conjugates; for peroxidase conjugates, 1,2-phenylenediamine or toluidine are commonly used. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted above. A solution containing the appropriate substrate is then added to the tertiary complex. The substrate reacts with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an evaluation of the amount of TRPV3, TRPV4 or TRPM8 protein which is present in the tissue sample.

[0133] Alternately, fluorescent compounds, such as fluorescein and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labeled antibody absorbs the light energy, inducing a state of excitability in the molecule, followed by emission of the light at a characteristic longer wavelength. The emission appears as a characteristic color visually detectable with a light microscope. Immunofluorescence and EIA techniques are both very well-established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotopes, chemiluminescent or bioluminescent molecules may also be employed. It will be readily apparent to the skilled artisan how to vary the procedure to suit the required use.

[0134] The level of expression of mRNA corresponding to the TRPV3, TRPV4 and TRPM8 genes can be detected utilizing methods well-known to those skilled in the art, e.g., northern blotting, RT-PCR, real time quantitative PCR, high density arrays and other hybridization methods. Accordingly, in another embodiment, an assay capable of detecting the expression of one or more of TRPV3, TRPV4 or TRPM8 genes in a sample of tissue, preferably human tissue, is provided which comprises contacting a human tissue sample with an oligonucleotide, i.e., a primer, that is capable of hybridizing to a nucleic acid, particularly

a mRNA, that encodes TRPV3, TRPV4 or TRPM8. The oligonucleotide primer is generally from 10-20 nucleotides in length, but longer sequences can also be employed.

[0135] RNA can be isolated from the tissue sample by methods well-known to those skilled in the art as described, e.g., in Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc., 1:4.1.1-4.2.9 and 4.5.1-4.5.3 (1996).

[0136] One preferred method for detecting the level of mRNA transcribed from the TRPV3, TRPV3, and TRPM8 genes is RT-PCR. In this method, an mRNA species is first transcribed to complementary DNA (cDNA) with use of the enzyme reverse transcriptase. Methods of reverse transcribing RNA into cDNA are well-known and described in Sambrook et al., *supra*. The cDNA is then amplified as in a standard PCR reaction (referred to as PCR) which is described in detail in U.S. Patent Nos. 4,683,195; 4,683,202; and 4,800,159.

[0137] Briefly, in PCR, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target nucleic acid sequence. An excess of deoxynucleoside triphosphates are added to a reaction mixture along with a DNA polymerase, e.g., Taq polymerase. The primers will bind to the target nucleic acid and the polymerase will cause the primers to be extended along the target nucleic acid sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target nucleic acid to form reaction products, excess primers will bind to the target nucleic acid and to the reaction products and the process is repeated.

[0138] Another preferred method for detecting the level of mRNA transcripts obtained from more than one of the disclosed genes involves hybridization of labeled mRNA to an ordered array of oligonucleotides. Such a method allows the level of transcription of a plurality of these genes to be determined simultaneously to generate gene expression profiles or patterns. In particularly useful embodiments, a gene expression profile derived from a tissue sample obtained from a subject suffering from pain can be compared with a gene expression profile derived from a sample obtained from a normal subject, i.e., a subject not suffering from pain, to determine whether one or more of the TRPV3, TRPV4 and TRPM8 genes are over-expressed in the sample obtained from the subject suffering from pain relative to the genes in the sample obtained from the normal subject, and thereby determine

which gene is responsible for the pain. Ligase chain reaction is another assay that is suitable for detecting the presence of a TRPV3, TRPV4, or TRPM8 polynucleotide.

[0139] The oligonucleotides utilized in this hybridization method typically are bound to a solid support. Examples of solid supports include, but are not limited to, membranes, filters, slides, paper, nylon, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, polymers, polyvinyl chloride dishes, etc. Any solid surface to which the oligonucleotides can be bound, either directly or indirectly, either covalently or non-covalently, can be used. A particularly preferred solid substrate is a high density array or DNA chip. These high density arrays contain a particular oligonucleotide probe in a pre-selected location on the array. Each pre-selected location can contain more than one molecule of the particular probe. Because the oligonucleotides are at specified locations on the substrate, the hybridization patterns and intensities (which together result in a unique expression profile or pattern) can be interpreted in terms of expression levels of particular genes.

[0140] The oligonucleotide probes are preferably of sufficient length to specifically hybridize only to complementary transcripts of the above identified gene(s) of interest. As used herein, the term "oligonucleotide" refers to a single-stranded nucleic acid. Generally the oligonucleotides probes will be at least 16-20 nucleotides in length, although in some cases longer probes of at least 20-25 nucleotides will be desirable.

[0141] The oligonucleotide probes can be labeled with one or more labeling moieties to permit detection of the hybridized probe/target polynucleotide complexes. Labeling moieties can include compositions that can be detected by spectroscopic, biochemical, photochemical, bioelectronic, immunochemical, electrical optical or chemical means. Examples of labeling moieties include, but are not limited to, radioisotopes, e.g., ^{32}P , ^{33}P , ^{35}S , chemiluminescent compounds, labeled binding proteins, heavy metal atoms, spectroscopic markers, such as fluorescent markers and dyes, linked enzymes, mass spectrometry tags and magnetic labels.

[0142] Oligonucleotide probe arrays for expression monitoring can be prepared and used according to techniques which are well-known to those skilled in the art as described, e.g., in Lockhart et al., *supra*; McGall et al., *supra*; and U.S. Patent No. 6,040,138.

[0143] In another aspect, kits are provided for detecting the level of expression of one or more of the TRPV3, TRPV4 and TRPM8 genes in a sample of tissue, e.g., a sample of tissue from a site of pain. For example, the kit can comprise a labeled compound or agent capable of detecting a protein encoded by, or mRNA corresponding to, at least one of the genes TRPV3, TRPV4 and TRPM8; or fragment of the protein, means for determining the amount of protein encoded by or mRNA corresponding to the gene or fragment of the protein; and means for comparing the amount of protein encoded by or mRNA corresponding to the gene or fragment of the protein, obtained from the subject sample with a standard level of expression of the gene, e.g., from a sample obtained from a subject not suffering pain. With respect to detection of TRPV3, TRPV4 and TRPM8 proteins, the agent can be an antibody specific for these proteins. With respect to detection of mRNA, the agent can be pre-selected primer pairs that selectively hybridize to mRNA corresponding to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 18. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect protein encoded by or mRNA corresponding to the gene.

[0144] In another aspect, the present invention is based on the identification of novel genes that are specific for trkA^+ pain-specific DRG neurons. DRG neurons can be classified into several distinct subpopulations with different functional, biochemical and morphological characteristics. The only known early markers differentially expressed by the DRG subtypes are the trk family of neurotrophin receptors. Gene-targeted deletion of the mouse neurotrophins and trks (receptor tyrosine kinases) have demonstrated that neurotrophin signaling is required for the survival of the different subpopulations of DRG neurons that trks specifically mark. For example, trkA knockout mice lack the nociceptive and thermoceptive neurons that sense pain and temperature.

Identification of Agonists and Antagonists

[0145] In another aspect, the present invention relates to the use of the TRPV3, TRPV4 and TRPM8 genes in methods for identifying agents useful in treating pain, or modulating responses to heat and cold, as flavor enhancers (e.g., menthol mimetics that one can identify using TRPM8 in a screening assay) and as cosmetic additives that provide a

cool or warm sensation to the skin (e.g., menthol mimetics, capsaicin mimetics or other compounds identified using TRPM8 or TRPV3 in screening assays). These methods comprise assaying for the ability of various agents to bind and/or modulate the activity of the proteins encoded by these genes, and/or decrease or increase the level of expression of mRNA corresponding to or protein encoded by these genes. The candidate agent may function as an antagonist or agonist. Examples of various candidate agents include, but are not limited to, natural or synthetic molecules such as antibodies, proteins or fragments thereof, antisense nucleotides, double-stranded RNA, ribozymes, organic or inorganic compounds, etc. Methods for identifying such candidate agents can be carried out in cell-based systems and in animal models.

[0146] For example, proteins encoding these genes expressed in a recombinant host cell such as CHO or COS may be used to identify candidate agents that bind to and/or modulate the activity of the protein, or that increase or decrease the level of expression of mRNA corresponding to or encoded by these genes. In this regard, the specificity of the binding of a candidate agent showing affinity for the protein can be shown by measuring the affinity of the agents for cells expressing the receptor or membranes from these cells. This can be achieved by measuring the specific binding of labeled, e.g., radioactive agent to the cell, cell membranes or isolated protein, or by measuring the ability of the candidate agent to displace the specific binding of standard labeled ligand.

[0147] Cells expressing proteins encoded by these genes can also be utilized to identify agents that modulate the protein's activity. For example, one method for identifying compounds useful for treating pain, or for use as a flavor or fragrance, comprises, providing a cell that expresses one of these proteins, e.g., TRPV3, TRPV4 or TRPM8, combining a candidate agent with the cell and measuring the effect of the candidate agent on the protein's activity. The cell can be a mammalian cell, a yeast cell, bacterial cell, insect cell or any other cell expressing the TRPV3 protein. The candidate compound is evaluated for its ability to elicit an appropriate response, e.g., the stimulation of cellular depolarization or increase in intracellular calcium ion levels due to calcium ion influx.

[0148] The level of intracellular calcium can be assessed using a calcium ion-sensitive fluorescent indicator such as a calcium ion-sensitive fluorescent dye, including, but not limited to, quin-2 (see, e.g., Tsien et al., *J. Cell Biol.*, 94:325 (1982)), fura-2 (see, e.g., Grynkiewicz et al., *J. Biol. Chem.*, 260:3440 (1985)), fluo-3 (see, e.g., Kao et al., *J. Biol.*

Chem., 264:8179 (1989)) and rhod-2 (see, e.g., Tsien et al., *J. Biol. Chem.*, Abstract 89a (1987)).

[0149] Membrane depolarization of recombinant cells expressing the above proteins can be monitored using a fluorescent dye that is sensitive to changes in membrane potential, including, but not limited to, carbocyanines such as 3,3'-dipentylloxacarbocyanine iodide (DiOC₅) and 3,3'-dipropylthiadicarbocyanine iodide (DiSC₃), oxonols, such as bis-(1,3-dibutylbarbituric acid) pentamethine oxonol (DiBAC₄ (Biotrend Chemikalien GmbH, Cologne, Germany)) or bis-(1,3-dibutylbarbituric acid) pentamethine oxonol, etc. Cellular fluorescence can be monitored using a fluorometer.

[0150] The assays to identify antagonists of ion channel activity are preferably performed under conditions in which the particular ion channel is active. Conversely, when seeking to identify an agonist, one would preferably perform the screening under conditions in which the ion channel is not active in the absence of the agonist. For example, TRPV3 is activated (i.e., mediates ion passage through a membrane) at temperatures of about 33°C and above. Accordingly, it is preferred to screen for antagonists of TRPV3 at a temperature of above about 33°C (e.g., 35°, 40°, 45°, or above), and to screen for agonists of TRPV3 at a temperature below 33°C (e.g., 30°, 25°, 20°C, or below). In some assays, it is desirable to discriminate between TRPV3-mediated ion transport and ion transport mediated by a different TRP ion channel. For example, to discriminate between TRPV3-mediated cation transport and cation transport mediated by, for example, TRPV1 or TRPV2, the assay can be conducted at a temperature above the activation threshold of TRPV3 but below the activation threshold of the other receptor (e.g., below about 43°C or below about 52°C, respectively, for TRPV1 and TRPV2). Thus, an assay temperature of between about 35°C and about 40°C would result in active TRPV3, but inactive TRPV1 and TRPV2.

[0151] Similarly, assays to identify antagonists of TRPM8 cation channel activity are preferably conducted under conditions in which the TRPM8 conducts cations in the absence of an antagonist. For example, since the threshold activation temperature of TRPM8 is approximately 15°C, one could screen for antagonists at a temperature below 15°C (e.g., 10°, 5°, 0°C, and the like). TRPM8 also is activated by menthol, so instead of or in addition to regulating activity by temperature, one could conduct the assay for antagonists in the presence of menthol. To identify an agonist of TRPM8, it is preferred to conduct the assay under conditions in which TRPM8 does not exhibit significant ion channel activity, such as a

temperature above 15°C (e.g., 20°C, 25°C, 30°C, etc.). To distinguish between TRPM8-mediated cation channel activity and that of other TRP ion channels, the assay for agonists can be conducted at a temperature below 33°C (the activation temperature of TRPV3). For example, a temperature between 20°C and 30°C would result in TRPM8 being inactive in the
5 absence of an agonist, and TRPV3, TRPV1 and TRPV2 also being inactive.

[0152] The TRPV3, TRPV4, and TRPM8 cation channels function to transport not only divalent cations (e.g., Ca^{2+}), but also monovalent cations (e.g., Na^+ , K^+).

[0153] The assay can be carried out manually or using an automated system. For high throughput screening assays to identify ligands of such proteins, an automated system is
10 preferred. For example, one type of automated system provides a 96-well, 384-well, or 1536-well, culture plate wherein a recombinant cell comprising a nucleotide sequence encoding such a protein is cultured to express the protein. The plate is loaded into a fluorescence imaging plate reader (e.g., "FLIPR[®]" commercially available from Molecular Devices Corp., Sunnyvale, CA) which measure the kinetics of intracellular calcium influx in
15 each of the wells. The FLIPR[®] can quantitatively transfer fluids into and from each well of the plate and thus can be utilized to add the calcium-ion sensitive fluorescent indicator dye, a candidate agent, etc. Membrane potential dyes suitable for high throughput assays include the FLIPR[®] Membrane Potential Assay Kit as sold by Molecular Devices Corp.

[0154] Once a candidate compound is identified as an agonist, such agonists can
20 be added to cells expressing such proteins followed by the addition of various candidate agents to determine which agents function as antagonists.

[0155] The nucleic acids and polypeptides of the present invention can also be utilized to identify candidate agents that modulate, i.e., increase or decrease the level of expression of mRNA and proteins in cells expressing these proteins. For example,
25 expression of the TRPV4 gene is shown to be up-regulated in a rat injury model (see Example 3). The level of expression of mRNA and protein can be detected utilizing methods well-known to those skilled in the art as described above.

[0156] After initial screening assays have identified agents that inhibit the protein's activity or level of expression of mRNA or protein, these agents can then be
30 assayed in conventional live animal models of pain to assess the ability of the agent to ameliorate the pathological effects produced in these models and/or inhibit expression levels of mRNA or protein. For example, in the case of the TRPV4 gene which is shown to be up-

regulated in a rat injury model, one method for identifying an agent useful in the treatment of pain comprises:

a) administering a candidate agent, e.g., an antisense nucleotide derived from the sequence of the TRPV4 gene, to a subject such as a rat model of pain; and

5 b) determining reversal of established pain in the animal. Various animal models utilized in neuropathic pain are well-known in the art, e.g., the partial sciatic ligation model, i.e., the Seltzer model, the chronic constriction injury model, i.e., the CCI model and the spinal nerve ligation model, i.e., the Chung model.

[0157] For example, in the partial sciatic ligation (see, the Seltzer model as
10 described in Seltzer et al., *Pain*, 43:205-218 (1990)), rats are anesthetized and a small incision made mid-way up one thigh (usually the left) to expose the sciatic nerve. The nerve is carefully cleared of surrounding connective tissues at a site near the trochanter just distal to the point at which the posterior biceps semitendinosus nerve branches off the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting
15 mini-needle, and tightly ligated so that the dorsal 1/3 to 1/2 of the nerve thickness is held within the ligature. The muscle and skin are closed with sutures and clips and the wound dusted with antibiotic powder. In sham animals the sciatic nerve is exposed but not ligated and the wound closed as before.

[0158] In the chronic constriction model (the CCI model as described in Bennett
20 et al., *Pain*, 33:87-107 (1988)) rats are anesthetized and a small incision is made midway up one thigh to expose the sciatic nerve. The nerve is freed of surrounding connective tissue and four ligatures of chromic gut are tied loosely around the nerve with approximately 1 mM between each, so that the ligatures just barely construct the surface of the nerve. The wound is closed with sutures and clips. In sham animals the sciatic nerve is exposed but not ligated
25 and the wound is closed.

[0159] In the spinal nerve ligation (see, the Chung model as described in Kim et al., *Pain*, 50:355-363 (1992)) rats are anesthetized and placed into a prone position and an incision made to the left of the spine at the L4-S2 level. A deep dissection through the paraspinal muscles and separation of the muscles from the spinal processes at the L4-S2
30 level will reveal part of the sciatic nerve as it branches to form the L4, L5 and L6 spinal nerves. The L6 transverse process is carefully removed with a small rongeur enabling visualization of these spinal nerves. The L5 spinal nerve is isolated and tightly ligated with

7-0 silk suture. The wound is closed with a single muscle suture (6-0 silk) and one or two skin closure clips and dusted with antibiotic powder. In sham animals the L5 nerve is exposed as before but not ligated and the wound closed as before.

[0160] Male Wistar rats (120-140 g) are used for each of the three models.

- 5 Mechanical hyperalgesia is then assessed in rat by measuring paw withdrawal thresholds of both hindpaws to an increasing pressure stimulus using an Analgesymeter (Ugo-Basile, Milan). Thermal hyperalgesia is assessed by measuring withdrawal latencies to a noxious thermal stimuli applied to the underside of each hindpaw. With all models, mechanical hyperalgesia and allodynia and thermal hyperalgesis develop within 1-3 days following
- 10 surgery and persist for at least 50 days. Reversal of mechanical hyperalgesia and allodynia and thermal hyperalgesia is assessed following administration of the agent, e.g., the antisense nucleotide specific for the TRPV4 gene.

[0161] Another example of a method for identifying agents useful in treating pain comprises:

- 15 a) administering a candidate agent to a subject such as a rat model of pain;
- b) detecting a level of expression of a protein encoded by or mRNA corresponding to one of genes described herein, e.g., TRPV4, in a sample obtained from the subject; and
- c) comparing the level of expression of the protein or mRNA in the sample in the presence of the agent with a level of expression of the protein or mRNA obtained from the
- 20 sample of the subject in the absence of the agent, wherein a decreased level of expression of the protein or mRNA in the sample in the presence of the agent relative to the level of expression of the protein or mRNA in the absence of the agent is indicative that the agent is useful in the treatment of pain.

[0162] The present invention also provides a method for identifying an agent

25 useful in the modulation of a mammalian sensory response. The method comprises

- a) contacting a candidate agent with a test system that comprises a receptor polypeptide selected from the group consisting of TRPM8, TRPV3, and TRPV4; and
- b) detecting a change in activity of the receptor polypeptide in the presence of the candidate agent as compared to the activity of the receptor polypeptide in the absence of the
- 30 agent, thereby identifying an agent that modulates receptor activity.

[0163] In particularly useful embodiments of this method, the sensory response is response to cold and the polypeptide is a TRPM8 polypeptide preferably having an amino

acid sequence selected from the group consisting of SEQ ID NO: 8 and SEQ ID NO: 11.

The method can further include the step of administering the agent that modulates receptor activity to a test subject, and thereafter detecting a change in the sensory response in the test subject.

5 [0164] The test system that is contacted with a candidate agent can comprise, e.g., a membrane that comprises the receptor polypeptide or a cell that expresses a heterologous polynucleotide that encodes the receptor polypeptide. In a useful embodiment, the heterologous polynucleotide comprises a nucleotide sequence as set forth in nucleotides 448-3762 of SEQ ID NO: 7 or as set forth in nucleotides 61-4821 of SEQ ID NO: 10, and the
10 receptor polypeptide is a TRPM8 polypeptide. The cell can be substantially isolated wherein the step of contacting of the cell with the candidate agent is performed *in vitro* or the cell can be present in an organism wherein the step of contacting is performed *in vivo*.

 [0165] In particularly useful embodiments, the receptor activity comprises increased or decreased Ca^{2+} passage through the membrane comprising the receptor
15 polypeptide, wherein the membrane can be, e.g., a substantially purified cell membrane or a membrane comprising a liposome.

Pharmaceutical Compositions and Methods

 [0166] The present invention also provides for therapeutic methods of treating a subject suffering from pain utilizing the aforementioned genes, i.e., TRPV3, TRPV4, and
20 TRPM8. Examples of suitable therapeutic agents include, but are not limited to, antisense nucleotides, ribozymes, double-stranded RNAs, antagonists and agonists, as described in detail below.

 [0167] As used herein, the term “antisense” refers to nucleotide sequences that are complementary to a portion of an RNA expression product of at least one of the disclosed
25 genes. “Complementary” nucleotide sequences refer to nucleotide sequences that are capable of base-pairing according to the standard Watson-Crick complementary rules. That is, purines will base pair with pyrimidine to form combinations of guanine:cytosine and adenine:thymine in the case of DNA, or adenine:uracil in the case of RNA. Other less common bases, e.g., inosine, 5-methylcytosine, 6-methyladenine, hypoxanthine and others
30 may be included in the hybridizing sequences and will not interfere with pairing.

[0168] When introduced into a host cell, antisense nucleotide sequences specifically hybridize with the cellular mRNA and/or genomic DNA corresponding to the gene(s) so as to inhibit expression of the encoded protein, e.g., by inhibiting transcription and/or translation within the cell.

5 [0169] The isolated nucleic acid molecule comprising the antisense nucleotide sequence can be delivered, e.g., as an expression vector, which when transcribed in the cell, produces RNA which is complementary to at least a unique portion of the encoded mRNA of the gene(s). Alternatively, the isolated nucleic acid molecule comprising the antisense nucleotide sequence is an oligonucleotide probe which is prepared *ex vivo* and, which when
10 introduced into the cell results in inhibiting expression of the encoded protein by hybridizing with the mRNA and/or genomic sequences of the gene(s).

[0170] Preferably, the oligonucleotide contains artificial internucleotide linkages which render the antisense molecule resistant to exonucleases and endonucleases, and thus are stable in the cell. Examples of modified nucleic acid molecules for use as antisense
15 nucleotide sequences are phosphoramidate, phosphorothioate and methylphosphonate analogs of DNA as described, e.g., in U.S. Patent Nos. 5,176,996; 5,264,564; and 5,256,775. General approaches to preparing oligomers useful in antisense therapy are described, e.g., in Van der Krol., *BioTechniques*, 6:958-976 (1988); and Stein et al., *Cancer Res.*, 48:2659-2668 (1988).

20 [0171] Typical antisense approaches, involve the preparation of oligonucleotides, either DNA or RNA, that are complementary to the encoded mRNA of the gene. The antisense oligonucleotides will hybridize to the encoded mRNA of the gene and prevent translation. The capacity of the antisense nucleotide sequence to hybridize with the desired gene will depend on the degree of complementarity and the length of the antisense
25 nucleotide sequence. Typically, as the length of the hybridizing nucleic acid increases, the more base mismatches with an RNA it may contain and still form a stable duplex or triplex. One skilled in the art can determine a tolerable degree of mismatch by use of conventional procedures to determine the melting point of the hybridized complexes.

[0172] Antisense oligonucleotides are preferably designed to be complementary to
30 the 5' end of the mRNA, e.g., the 5'untranslated sequence up to and including the regions complementary to the mRNA initiation site, i.e., AUG. However, oligonucleotide sequences that are complementary to the 3' untranslated sequence of mRNA have also been shown to

be effective at inhibiting translation of mRNAs as described e.g., in Wagner, *Nature*, 372:333 (1994). While antisense oligonucleotides can be designed to be complementary to the mRNA coding regions, such oligonucleotides are less efficient inhibitors of translation.

[0173] Regardless of the mRNA region to which they hybridize, antisense oligonucleotides are generally from about 15 to about 25 nucleotides in length.

[0174] The antisense nucleotide can also comprise at least one modified base moiety, e.g., 3-methylcytosine, 5-methylcytosine, 7-methylguanine, 5-fluorouracil, 5-bromouracil and may also comprise at least one modified sugar moiety, e.g., arabinose, hexose, 2-fluorarabinose and xylulose.

[0175] In another embodiment, the antisense nucleotide sequence is an alpha-anomeric nucleotide sequence. An alpha-anomeric nucleotide sequence forms specific double stranded hybrids with complementary RNA, in which, contrary to the usual beta-units, the strands run parallel to each other as described e.g., in Gautier et al., *Nucl. Acids. Res.*, 15:6625-6641 (1987).

[0176] Antisense nucleotides can be delivered to cells which express the described genes *in vivo* by various techniques, e.g., injection directly into the target tissue site, entrapping the antisense nucleotide in a liposome, by administering modified antisense nucleotides which are targeted to the target cells by linking the antisense nucleotides to peptides or antibodies that specifically bind receptors or antigens expressed on the cell surface.

[0177] However, with the above-mentioned delivery methods, it may be difficult to attain intracellular concentrations sufficient to inhibit translation of endogenous mRNA. Accordingly, in a preferred embodiment, the nucleic acid comprising an antisense nucleotide sequence is placed under the transcriptional control of a promoter, i.e., a DNA sequence which is required to initiate transcription of the specific genes, to form an expression construct. The use of such a construct to transfect cells results in the transcription of sufficient amounts of single-stranded RNAs to hybridize with the endogenous mRNAs of the described genes, thereby inhibiting translation of the encoded mRNA of the gene. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of the antisense nucleotide sequence. Such vectors can be constructed by standard recombinant technology methods. Typical expression vectors include bacterial plasmids or phage, such as those of the pUC or BluescriptTM plasmid series, or viral vectors

such as adenovirus, adeno-associated virus, herpes virus, vaccinia virus and retrovirus, adapted for use in eukaryotic cells. Expression of the antisense nucleotide sequence can be achieved by any promoter known in the art to act in mammalian cells. Examples of such promoters include, but are not limited to, the promoter contained in the 3' long terminal repeat of Rous sarcoma virus as described, e.g., in Yamamoto et al., *Cell*, 22:787-797 (1980); the herpes thymidine kinase promoter as described, e.g., in Wagner et al., *Proc. Natl. Acad. Sci. USA*, 78:1441-1445 (1981); the SV40 early promoter region as described e.g., in Bernoist and Chambon, *Nature*, 290:304-310 (1981); and the regulatory sequences of the metallothionein gene as described, e.g., in Brinster et al., *Nature*, 296:39-42 (1982).

[0178] Ribozymes are RNA molecules that specifically cleave other single-stranded RNA in a manner similar to DNA restriction endonucleases. By modifying the nucleotide sequences encoding the RNAs, ribozymes can be synthesized to recognize specific nucleotide sequences in a molecule and cleave it as described, e.g., in Cech, *J. Amer. Med. Assn.*, 260:3030 (1988). Accordingly, only mRNAs with specific sequences are cleaved and inactivated.

[0179] Two basic types of ribozymes include the "hammerhead" type as described, e.g., in Rossie et al., *Pharmac. Ther.*, 50:245-254 (1991); and the hairpin ribozyme as described, e.g., in Hampel et al., *Nucl. Acids Res.*, 18:299-304 (1999) and U.S. Patent No. 5,254,678. Intracellular expression of hammerhead and hairpin ribozymes targeted to mRNA corresponding to at least one of the disclosed genes can be utilized to inhibit protein encoded by the gene.

[0180] Ribozymes can either be delivered directly to cells, in the form of RNA oligonucleotides incorporating ribozyme sequences, or introduced into the cell as an expression vector encoding the desired ribozymal RNA. Ribozyme sequences can be modified in essentially the same manner as described for antisense nucleotides, e.g., the ribozyme sequence can comprise a modified base moiety.

[0181] Double-stranded RNA, i.e., sense-antisense RNA, corresponding to at least one of the disclosed genes can also be utilized to interfere with expression of at least one of the disclosed genes. Interference with the function and expression of endogenous genes by double-stranded RNA has been shown in various organisms such as *C. elegans* as described e.g., in Fire et al., *Nature*, 391:806-811 (1998); *Drosophila* as described, e.g., in Kennerdell et al., *Cell*, 23:95(7):1017-1026 (1998); and mouse embryos as described, e.g., in Wianni et

al., *Nat. Cell Biol.*, 2(2):70-75 (2000). Such double-stranded RNA can be synthesized by *in vitro* transcription of single-stranded RNA read from both directions of a template and *in vitro* annealing of sense and antisense RNA strands. Double-stranded RNA can also be synthesized from a cDNA vector construct in which the gene of interest is cloned in opposing orientations separated by an inverted repeat. Following cell transfection, the RNA is transcribed and the complementary strands reanneal. Double-stranded RNA corresponding to at least one of the disclosed genes could be introduced into a cell by cell transfection of a construct such as that described above.

[0182] The term “antagonist” with respect to methods of treatment refers to a molecule which, when bound to the protein encoded by the gene, inhibits its activity. Antagonists can include, but are not limited to, peptides, proteins, carbohydrates and small molecules (generally, a molecule having a molecular weight of about 1000 daltons or less).

[0183] The term “agonist” with respect to methods of treatment refers to a molecule which, when bound to the protein encoded by the gene, activates its activity. Agonists can include, but are not limited to, peptides, proteins, carbohydrates and small molecules.

[0184] In a particularly useful embodiment, the antagonist is an antibody-specific for the cell-surface protein expressed by one of the genes, e.g., TRPV3. Antibodies useful as therapeutics encompass the antibodies as described above, and are preferably monoclonal antibodies. The antibody alone may act as an effector of therapy or it may recruit other cells to actually effect cell killing. The antibody may also be conjugated to a reagent such as a chemotherapeutic, radionuclide, ricin A chain, cholera toxin, pertussis toxin, etc. and serve as a target agent. Alternatively, the effector may be a lymphocyte carrying a surface molecule that interacts, either directly or indirectly, with a tumor target. Various effector cells include, cytotoxic T cells and NK cells.

[0185] Examples of the antibody-therapeutic agent conjugates which can be used in therapy include, but are not limited to: 1) antibodies coupled to radionuclides, such as ^{125}I , ^{131}I , ^{123}I , ^{111}In , ^{105}Rh , ^{153}Sm , ^{67}Cu , ^{67}Ga , ^{166}Ho , ^{177}Lu , ^{186}Re and ^{188}Re , and as described, e.g., in Goldenberg et al., *Cancer Res.*, 41:4354-4360 (1981); Carrasquillo et al., *Cancer Treat. Rep.*, 68:317-328 (1984); Zalcborg et al., *J. Natl. Cancer Inst.*, 72:697-704 (1984); Jones et al., *Int. J. Cancer*, 35:715-720 (1985); Lange et al., *Surgery*, 98:143-150 (1985); Kaltovich et al., *J. Nucl. Med.*, 27:897 (1986); Order et al., *Int. J. Radiother. Oncol. Biol.*

Phys., 8:259-261 (1982); Courtenay-Luck et al., *Lancet*, 1:1441-1443 (1984) and Ettinger et al., *Cancer Treat. Rep.*, 66:289-297 (1982); 2) antibodies coupled to drugs or biological response modifiers, such as methotrexate, adriamycin and lymphokines, such as interferon as described, e.g., in Chabner et al., *Cancer, Principles and Practice of Oncology*, J.B. Lippincott Co., Philadelphia, PA, 1:290-328 (1985); Oldham et al., *Cancer, Principles and Practice of Oncology*, J.B. Lippincott Co., Philadelphia, PA, 2:2223-2245 (1985); Deguchi et al., *Cancer Res.*, 46:3751-3755 (1986); Deguchi et al., *Fed. Proc.*, 44:1684 (1985); Embleton et al., *Br. J. Cancer*, 49:559-565 (1984); and Pimm et al., *Cancer Immunol. Immunother.*, 12:125-134 (1982); 3) antibodies coupled to toxins, as described, e.g., in Uhr et al., *Monoclonal Antibodies and Cancer*, Academic Press, Inc., pp. 85-98 (1983); Vitetta et al., *Biotechnology and Bio. Frontiers*, P.H. Abelson, Ed., pp. 73-85 (1984) and Vitetta et al., *Science*, 219:644-650 (1983); 4) heterofunctional antibodies, for example, antibodies coupled or combined with another antibody so that the complex binds both to the carcinoma and effector cells, e.g., killer cells, such as T cells, as described, e.g., in Perez et al., *J. Exper. Med.*, 163:166-178 (1986); and Lau et al., *Proc. Natl. Acad. Sci. USA*, 82:8648-8652 (1985); and 5) native, i.e., non-conjugated or non-complexed, antibodies, as described in, e.g., in Herlyn et al., *Proc. Natl. Acad. Sci. USA*, 79:4761-4765 (1982); Schulz et al., *Proc. Natl. Acad. Sci. USA*, 80:5407-5411 (1983); Capone et al., *Proc. Natl. Acad. Sci. USA*, 80:7328-7332 (1983); Sears et al., *Cancer Res.*, 45:5910-5913 (1985); Nepom et al., *Proc. Natl. Acad. Sci. USA*, 81:2864-2867 (1984); Koprowski et al., *Proc. Natl. Acad. Sci. USA*, 81:216-219 (1984); and Houghton et al., *Proc. Natl. Acad. Sci. USA*, 82:1242-1246 (1985).

[0186] Methods for coupling an antibody or fragment thereof to a therapeutic agent as described above are well-known in the art and are described, e.g., in the methods provided in the references above. In yet another embodiment, the antagonist useful as a therapeutic for treating disorders can be an inhibitor of a protein encoded by one of the disclosed genes.

[0187] In the case of treatment with an antisense nucleotide, the method comprises administering a therapeutically effective amount of an isolated nucleic acid molecule comprising an antisense nucleotide sequence derived from at least one of the disclosed genes, wherein the antisense nucleotide has the ability to decrease the transcription/translation of one of the genes. The term "isolated" nucleic acid molecule

means that the nucleic acid molecule is removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring nucleic acid molecule is not isolated, but the same nucleic acid molecule, separated from some or all of the coexisting materials in the natural system, is isolated, even if subsequently
5 reintroduced into the natural system. Such nucleic acid molecules could be part of a vector or part of a composition, and still be isolated in that such vector or composition is not part of its natural environment.

[0188] With respect to treatment with a ribozyme or double-stranded RNA molecule, the method comprises administering a therapeutically effective amount of a
10 nucleotide sequence encoding a ribozyme, or a double-stranded RNA molecule, wherein the nucleotide sequence encoding the ribozyme/double-stranded RNA molecule has the ability to decrease the transcription/translation of one of the genes.

[0189] In the case of treatment with an antagonist, the method comprises administering to a subject a therapeutically effective amount of an antagonist that inhibits a
15 protein encoded by one of these genes.

[0190] In the case of treatment with an agonist, the method comprises administering to a subject a therapeutically effective amount of an agonist that inhibits a protein encoded by one of these genes. In particularly useful embodiments, the gene is TRPV8 and the agonist can include compounds that are derivatives of menthol and other
20 compounds known to be cool-feeling agents including, but not limited to, camphor, thymol, peppermint oil, thymol and the like. Such compounds can be particularly useful in alleviating pain associated with skin inflammation by providing a cool sensation to the skin.

[0191] A "therapeutically effective amount" of an isolated nucleic acid molecule comprising an antisense nucleotide, nucleotide sequence encoding a ribozyme, double-
25 stranded RNA, agonist or antagonist, refers to a sufficient amount of one of these therapeutic agents to treat a subject suffering from pain. The determination of a therapeutically effective amount is well within the capability of those skilled in the art. For any therapeutic, the therapeutically effective dose can be estimated initially either in cell culture assays, or in animal models, usually mice, rats, rabbits, dogs or pigs. The animal model may also be used
30 to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

[0192] The present invention also provides for methods of treating pain, wherein the method comprises identifying a patient suffering from a TRPV3-, TRPV4- or TRPM8-mediated pain by measuring expression of protein encoded by or mRNA corresponding to the TRPV3, TRPV4 or TRPM8 gene, and then administering to such a patient an
5 analgesically effective amount of an agent which decreases or increases the activity or expression of one of these genes. The agent can be a therapeutic agent as described above.

[0193] An "analgesically effective amount" can be a therapeutically effective amount as described above.

[0194] Therapeutic efficacy and toxicity may be determined by standard
10 pharmaceutical procedures in cell cultures or experimental animals, e.g., ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Antisense nucleotides, ribozymes, double-stranded RNAs, agonists, antagonists and other agents which exhibit large therapeutic
15 indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient and the route of administration.

[0195] The exact dosage will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight and gender of the subject, diet, time and frequency of administration,
25 drug combination(s), reaction sensitivities and tolerance/response to therapy.

[0196] Normal dosage amounts may vary from 0.1-100,000 mg, up to a total dose of about 1 g, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for
30 antagonists.

[0197] For therapeutic applications, the antisense nucleotides, nucleotide sequences encoding ribozymes, double-stranded RNAs (whether entrapped in a liposome or

contained in a viral vector), antibodies or other agents are preferably administered as pharmaceutical compositions containing the therapeutic agent in combination with one or more pharmaceutically acceptable carriers. The compositions may be administered alone or in combination with at least one other agent, such as stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier, including, but not limited to, saline, buffered saline, dextrose and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs or hormones.

[0198] The pharmaceutical compositions may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intraarticular, intraarterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual or rectal means.

[0199] In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co., Easton, PA.

[0200] Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well-known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for ingestion by the patient.

[0201] Pharmaceutical preparations for oral use can be obtained through combination of active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate.

[0202] Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

[0203] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid or liquid polyethylene glycol with or without stabilizers.

[0204] Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers, such as Hank's solution, Ringer's solution or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil or synthetic fatty acid esters, such as ethyl oleate or triglycerides or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0205] For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0206] The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0207] The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation
5 may be a lyophilized powder which may contain any or all of the following: 1-50 mM histidine, 0.1-2% sucrose, and 2-7% mannitol, at a pH range of 4.5-5.5, that is combined with buffer prior to use.

[0208] After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For
10 administration of the antisense nucleotide or antagonist, such labeling would include amount, frequency and method of administration. Those skilled in the art will employ different formulations for antisense nucleotides than for antagonists, e.g., antibodies or inhibitors. Pharmaceutical formulations suitable for oral administration of proteins are described, e.g., in U.S. Patent Nos. 5,008,114; 5,505,962; 5,641,515; 5,681,811; 5,700,486;
15 5,766,633; 5,792,451; 5,853,748; 5,972,387; 5,976,569; and 6,051,561.

[0209] In another aspect, the treatment of a subject, e.g., a rat injury model, with a therapeutic agent such as those described above, can be monitored by detecting the level of expression of mRNA or protein encoded by at least one of the disclosed genes, or the activity of the protein encoded by the gene. These measurements will indicate whether the
20 treatment is effective or whether it should be adjusted or optimized. Accordingly, one or more of the genes described herein can be used as a marker for the efficacy of a drug during clinical trials.

[0210] In a particularly useful embodiment, a method for monitoring the efficacy of a treatment of a subject suffering from pain with an agent (e.g., an antagonist, protein,
25 nucleic acid, small molecule or other therapeutic agent or candidate agent identified by the screening assays described herein) is provided comprising:

- a) obtaining a pre-administration sample from a subject prior to administration of the agent;
- b) detecting the level of expression of mRNA or protein encoded by the gene, or
30 activity of the protein encoded by the gene in the pre-administration sample;
- c) obtaining one or more post-administration samples from the subject;

d) detecting the level of expression of mRNA or protein encoded by the gene, or activity of the protein encoded by the gene in the post-administration sample or samples;

e) comparing the level of expression of expression of mRNA or protein encoded by the gene, or activity of the protein encoded by the gene in the pre-administration sample with the level of expression of mRNA or protein encoded by the gene, or activity of the protein encoded by the gene in the post-administration sample or samples; and

f) adjusting the administration of the agent accordingly.

[0211] For example, increased administration of the agent may be desirable to decrease the level of expression or activity of the gene to lower levels than detected, i.e., to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to increase expression or activity of the gene to higher levels than detected, i.e., to decrease the effectiveness of the agent.

EXAMPLES

[0212] The following examples are offered to illustrate, but not to limit the present invention.

EXAMPLE 1

Identification of New VRs

A. VR searching

[0213] Strategy: Known VR sequences are downloaded (GI Nos. 6782444, 5305598, 7106445, 4589143, 6635238, 2570933, 5263196 and 4589141) from NCBI and assembled using Clustal (Megalign--DNASTar, Madison, WI) with the following parameters: Gap Penalty 10, GapLength Penalty 10, Ktuple 1, Window 5 and Diagonals Saved 5. This alignment is saved as a *.MSF file.

[0214] This *.MSF file is converted to a hidden Markov model using HMMBUILD 2.0 (Sean Eddy, Washington University, St. Louis) then calibrated using HMMCALIBRATE 2.0 (Sean Eddy), and used to search 6 frame translations (Feb 20 release) of the Celera human genome data using the default parameters. The protein sequences of these files are retrieved and used as subjects in a BLASTP search of NR. This file is manually inspected identifying three novel candidates for VRs.

B. Identification of VR TRPV3

[0215] Mechanical and thermal stimuli activate specialized sensory neurons that terminate in the skin at receptor structures like hair follicles or as free nerve endings. Pain and temperature sensitive neurons belong to the latter category and are thus thought to directly sense stimuli. A TRP channel that is expressed in pain neurons, VR1 is partially responsible for the detection of noxious heat. This Example describes the cloning of TRPV3, a close relative of VR1 that is also activated by noxious heat. Surprisingly, TRPV3 is most highly-expressed in skin cells. Keratinocytes that express TRPV3 show a calcium influx in response to noxious heat. Therefore, skin cells possess molecular tools similar to those of sensory neurons to “sense” heat.

[0216] VR1 (TRPV1), the best-characterized receptor in the somatic sensory system, is directly gated by noxious heat. VR1 is expressed in small-diameter, nociceptive DRG neurons that terminate in the skin as free nerve endings to detect noxious heat. Analysis of VR1 knockout mice has demonstrated that this channel is partially responsible for heat sensitivity. VR1 belongs to the family of six transmembrane-containing TRP non-selective cation-channels that function in mechanosensation, osmoregulation and replenishment of intracellular calcium stores. This TRPV family includes at least five members, three of which are expressed in DRG neurons. One of these, VRL1 (TRPV2), is also gated by heat, but has a higher threshold than VR1 (52°C instead of 43°C) and is not co-expressed with VR1. Recent experiments have implied that VRL1 expression does not correlate with the heat-sensitive neurons in VR1 knockout mice, suggesting the existence of yet another heat-sensing channel.

[0217] Public and Celera databases for VR1-related TRP channels are searched by constructing a Hidden Markov Model (HMM) of the VR1 and VRL1 protein sequences from different mammalian species. With this model, the 6-frame translation of human sequence is queried and has identified multiple new putative exons with a great degree of sequence similarity to the ankyrin and transmembrane domains of VR1. These exons map to two genes, one of which is TRPV4, as described, e.g., in Liedtke et al., *Cell*, 103:525-35 (2000); and Strotmann et al., *supra*). The other novel gene is known as TRPV3.

[0218] The full-length sequence of mouse TRPV3 is derived from a combination of exon-prediction software, PCR and RACE amplification from newborn mouse DRG and skin cDNA. For PCR cloning, primers (5'-TGACATGATCCTGCTGAGGAGTG-3'

(SEQ ID NO: 19) and 5'-ACGAGGCAGGCGAGGTATTCTT-3' (SEQ ID NO: 20)) are designed from the HMM sequences for TRPV3 as a result of blast hits to the ankyrin and transmembrane domains and used to amplify a 699-nucleotide fragment of TRPV3 from newborn DRG cDNA. From this initial fragment, Rapid Amplification of cDNA Ends (RACE) PCR (Clontech) is used to obtain the 5' and 3' ends of TRPV3 from mouse newborn skin and DRG cDNA. In order to characterize the genomic locus of VR1 and TRPV3, primers are designed from predicted HMM TRPV3 exon sequences and used to screen a genomic BAC Mouse (RPCI22) library (Roswell Park Cancer Institute). Primers utilized are shown in Table 1. Additionally, mouse VR1 BACs are identified by hybridizing a 320 bp probe spanning the mouse VR1 ankyrin region to the same BAC library. Positive BAC clones are further characterized by restriction digest mapping, pulse field gel electrophoresis, and Southern blotting as previously described using probes specific to the 5' and 3' ends of the VR1 and TRPV3 genes. BAC clones positive for TRPV3 included 5J3. BAC clones that were positive for both VR1 and TRPV3 included 9e22, 27I14, 82c1 and 112g17. BACs positive for VR1 included 137N13, 137O13, 234J23, 246D9 and 285G11.

Table 1: TRPV3 Primers

		SEQ ID NO:
5' RACE		
AP40	CAGCGTATGCAGAGGCTCCAGGGTCAG	21
AP4	TTGAAGTCCTCAGCCACCGTCACCA	22
Mvr4ANK	CACCAGCGCGTGCAGGATGT	23
AP105 RACE-rev	tcgttctcctcagcgaaggcaagcaga	24
AP110R (nested)	CCTTCTATCTCCAGGAAGAAGTGTGC	25
ap113r (race)	GTCACCAGCGCGTGCAGGATGTTGT	26
ap36	AGGCCCATACGCCAGTCCGTGAAC	27
ap33R	CATGCCCATAGACTGGAAGCC	28
ap71	GATGGCGATGTTTCAGCGCTGTCTGC	29
3' RACE		
AP37	GCTGCCAAGATGGGCAAGGCTGAGA	30
Ap31	CCTGGGCTGGGCGAACATGCTCTA	31
TM6VR4RACE	GCGCCAGATGCGTTCACTTTCTTTGGA	32
Primers to amplify partial and/or full-length TRPV transcript		SEQ ID NO:
mVR4-F	TGACATGATCCTGCTGAGGAGTG	33
mVR4-R	ACGAGGCAGGCGAGGTATTCTT	34

AP72 F	TCCAAGCTGTGCTTGTGATA	35
AP73R	CTTGAGCATGTAGTTTCACACAAA	36
AP74R	GTGTTTTCCATTCCGTCCAC	37
AP75R	CGACGTTTCTGGGAATTCAT	38
AP76R	CTTGAGCATGTAGTTTCACACAAA	39
AP77F	TCCTCCTCCTCAACATGCTC	40
AP78R	TGGAAATCAAAACAGTATTTCAATG	41
AP79F	CTCTTCAAGCTCACCATAGGC	42
AP80R	CGACGTTTCTGGGAATTCAT	43
AP81R	GTGTTTTCCATTCCGTCCAC	44
AP82R	CCCTCTGTTACCGCAGACAC	45
AP83F	ACTCCAGCCTGGGTGACA	46
AP84R	ATGGTCTCCAGCTCCCAGTT	47
AP85R	AGGAGGACGAAGGTGAGGAT	48
AP86F	AGCCTCAGGTCTGAAGTGGA	49
AP87R	GCCAGATGCGTTCACTTTCT	50
AP88R	GGCAAATTTCTTCCATTTCG	51
AP89R	AGATGCGTTCGCTCTCCTT	52
AP102F	TGCACACTTCTTCCTGGAGAT	53
AP103F	TTCCTCATGCACAAGCTGAC	54
AP104F	TCTTCCTGGAGATAGAAGGGATT	55
AP106R	CGATGATTTCCAGCACAGAG	56
AP107F	CTACCAATGTAGACACAACGAC	57
AP108F	TACCAGCATGAAGGCTTCTATTT	58
AP109R	ATAAGCACTGCTGTGATGTCTCC	59
AP111R	GTCAGCTTGTGCATGAGGAA	60
AP112F	TGACAGAGACCCCATCCAATCCCAACA	61
AP114F	CTCTTGTGATATGGCTTTCTGG	62
AP115F	GAGAAGGAGTGGGTGAGCTG	63
AP116R	CCTTCTCCAGAGTCCACAG	64
AP117F	AGCAGGCAGGAAAATGAGAG	65
AP118R	CCAAAGATGGTCCAGAAAGC	66
AP115F	CTCTTGTGATATGGCTTTCTGG	67
AP116F	AACTGTGATGACATGGACTCTCCCCCAG	68

AP118F	AACTGTGATGACATGGACTC	69
AP119F	CAGGATGATGTGACAGAGACCCCATC	70
AP128F	ATGATCCTGCTGAGGAGTGG	71
AP129R	AGGATGACACAGGCCCATAC	72
AP130F	ATCCTCACCTTCGTCCTCCT	73
AP131R	CATTCCGTCCACTTCACCTC	74
AP204R (3'UTR)	TGGTTTTGCTGTTGTTTCCTG	75
AP205R	(POLYA)CATGTAAATCAACGCAGAAGTCA	76

[0219] Several murine ESTs from skin tissues contain 3' UTR TRPV3 sequence (BB148735, BB148088, BB151430 and AI644701), and recently the human TRPV3 sequence has been annotated (see GI: 185877, 18587705 and Peng et al., *Genomics*, 76:99-109 (2001)).

[0220] As predicted from the nucleotide sequence, TRPV3 is composed of 791 amino acid residues. The overall sequence of mouse TRPV3 has 43% identity to TRPV1 (VR1) and TRPV4; 41% to TRPV2 (VRL1); and 20% to TRPV5 (ECAC) and TRPV6 (see Figure 2C). TRPV3 has four, instead of the usual three, predicted N-terminal ankyrin domains that are thought to be involved in protein-protein interactions, TM6 domains and a pore loop region between the last two membrane spanning regions. Two coiled-coil domains N-terminus to the ankyrin domains in TRPV3 are also identified (see Figure 2F). Coiled-coil domains are implicated in oligomerization of GABA-B channels, and have been previously reported to be present in some TRP channels, but not for TRPVs. Further examination shows that VR1, but not the other members of the TRPV family, also has putative coiled-coil domains in the same N-terminal location. Phylogenetic analysis illustrates that TRPV3 is indeed a member of the OTRP/TRPV sub-family, which is part of the larger TRP ion channel family (see Figure 2A). The same BAC genomic clone in the public database contains the sequence of TRPV3 and VR1. Both genes map to human chromosome 17p13 and mouse chromosome 11B4. Mapping analysis of these BAC clones, and later the assembled human and mouse genome sequences reveals the distance between the two genes to be about 10 kb (see Figure 2B). This suggests that TRPV3 and VR1 are derived from a single duplication event.

EXAMPLE 2

Localization of TRPV3 Expression

A. Northern blot analysis

[0221] For Northern blot analyses approximately 3 µg of polyA⁺ RNA extracted from adult mouse and newborn tissue are electrophoresed on 1% glyoxal gels, transferred and hybridized at high-stringency with a ³²P labeled probe representing the entire full-length TRPV3 sequence. Commercial Northern blots (Clontech) are hybridized with the same TRPV3 full-length probe. For human skin specific expression, Northern blots are prepared from 20 µg of total RNA from primary keratinocytes and cell lines CRL-2309 and CRL-2404 (ATCC) or from 2 µg of polyA⁺ adult and fetal skin RNA (Stratagene). Blots are hybridized with a probe corresponding to the ankryin 1-TM2 region of the TRPV3 human sequence. For VR1 hybridizations, a probe corresponding to nucleotides 60-605, encoding the amino terminus of rat VR1 are used on mouse blots. The entire coding sequence of human VR1 are used as a probe on human Northern blots.

[0222] As stated above, to determine the overall tissue distribution of TRPV3, the full-length mouse TRPV3 sequence is used as a probe for Northern blot analysis. No TRPV3 expression is detected using commercial Northern blots. Blots from adult rat are then used that include tissues relevant to somatic sensation, including DRG, spinal cord and different sources of skin. A mRNA of approximately 6.5 kb is present in tissues derived from skin but not in DRGs. Probing the same adult blot with a TRPV1-specific probe confirms its strong expression in DRG while demonstrating a lack of expression in skin tissues. Northern blot analysis of human adult and fetal skin also shows expression of TRPV3. Cultured primary mouse keratinocytes as well as several epidermal cell lines do not show any TRPV3 expression by Northern blots. These finding suggest that TRPV3 expression may get down regulated after tissue dissociation and long-term culture. Northern blots from newborn and adult mice that include tissues relevant for somatic sensation, including DRG, spinal cord and different sources in skin also show TRPV3 expression in skin tissues with weak expression in the DRG.

B. In situ hybridization

[0223] For *in situ* hybridizations, newborn and adult tissues are dissected, fixed in 4% paraformaldehyde in PBS, cryoprotected and frozen in liquid nitrogen in OCT mounting

medium. Cryostat sections (10 μm) are processed and probed with either a digoxigenin cRNA probe or a ^{35}S -labeled probe generated by *in vitro* transcription as described in Wilkinson, in *Essential Developmental Biology, A Practical Approach*, C. Stern, P. Holland, eds., Oxford Univ. Press, NY, pp. 258-263 (1993). Two mouse TRPV3-specific antisense
5 riboprobes are used, one corresponding to nucleotides 235-1020 encoding the amino terminus and the other spanning nucleotides 980-1675 corresponding to the region between the third ankyrin and TM4 domains.

[0224] Digoxigenin-labeled probes show specific expression in specialized skin tissues, such as hair follicles in both newborn and adult mice. Expression in epidermis is
10 difficult to assess, because of high background observed in this tissue with the sense probe. To circumvent this problem, and to gain more sensitivity, ^{35}S -radioactive *in situ* hybridizations are carried out on cross-sections of newborn mice. Clear expression is detected in the epidermis and hair follicles. No significant expression is detected in DRGs.

C. Immunohistochemical staining assays

15 [0225] For immunohistochemistry, rabbits are immunized (AnimalPharm Services, Healdsburg, CA) with KLH conjugated peptide corresponding to either the N-terminus of mouse TRPV3 (CDDMDSPQSPQDDVTETPSN (SEQ ID NO: 77)) or a C-terminus peptide (KIQDSSRSNSKTTL (SEQ ID NO: 78)). Affinity purified antiserum recognizes a band of relative molecular mass ~ 85 kDa in whole-cell extracts prepared from
20 CHO cells stably transfected with mouse TRPV3 (not shown). For peptide competition, diluted antibody solutions (1:5000) of TRPV3 are pre-incubated (room temperature, 2 hours) with TRPV3 antigenic peptide ($9 \mu\text{g/mL}^{-1}$) prior to incubation with tissue sections. Immunofluorescence are performed on fixed frozen and paraffin sections using rabbit anti-TRPV3 (1:5000), pan cytokeratin (Abcam) cytokeratin (1:300, Abcam), cytokeratin 10
25 (K8.60, Sigma), pan-basal Cytokeratin (Abcam), PGP9.5 (Abcam) followed by FITC-labeled goat anti-rabbit ($10 \mu\text{g/mL}^{-1}$) and Cy-3-labeled donkey anti-mouse (Jackson ImmunoResearch) antibodies.

[0226] Using polyclonal antibodies produced against TRPV3 peptides from either the N-terminus or the C-terminus, intense TRPV3 immunoreactivity is observed in most
30 keratinocytes at the epidermal layer and in hair follicles from newborn and adult rodent tissues. In the epidermis, staining is absent in the outermost layers (stratum corneum and

lucidum) as well as the basement membrane. In hair follicles, expression is localized to the outer root sheath and absent from the matrix cells, inner root sheath and sebaceous glands. Developmentally, expression in hair follicles increases from newborn to adult stages. High magnification of these images indicates staining in the cytoplasm and at high levels in the plasma membrane.

[0227] Coexpression with various keratinocyte-specific markers shows that TRPV3 is expressed in the basal keratinocytes, which *in vitro* require low calcium concentrations to maintain their undifferentiated state, as well as in some of the more differentiated suprabasal layers of the epidermis. Temperature-sensing neurons are thought to terminate as free nerve endings mainly at the level of dermis, but some processes do extend into the epidermis (see Hilliges et al., *supra*; and Cauna, *supra*. Cutaneous termini can be labeled with the immunohistochemical marker protein gene product 9.5 (PGP 9.5), and it is observed that these epidermal endings indeed co-localize with TRPV3.

D. GFP-fusion constructs

[0228] The full-length mouse TRPV3 is amplified and subcloned into pcDNA3.1/CT-GFP-TOPO (Invitrogen). *In vitro* transcription/translation (TnT System, Promega) confirms the integrity of the constructs. Cells are viewed live or fixed in 4% paraformaldehyde 48-72 hours after transfection, counterstained with propidium iodide and mounted in Slowfade (Molecular probes).

[0229] Confocal fluorescence microscopy on cells transiently transfected with a C-terminally GFP-tagged TRPV3 protein construct also finds the protein mainly localized at the plasma membrane. This pattern of expression at the cell membrane is consistent with TRPV3 having a role as an ion channel. In sum, the expression analysis suggests that TRPV3 is most prominently expressed in plasma membrane of keratinocytes in both rodents and humans.

EXAMPLE 3

Activation of TRPV3 Protein by Heat

A. Effect of heat, capsazepine and ruthenium red upon conductance

[0230] Given the high degree of homology of TRPV3 to TRPV family members, TRPV3 is tested to determine whether it responds to stimuli known to activate other closely-

related family members. Accordingly, the effects of heat upon TRPV3 activity in mediating conductance are examined using whole-cell patch-clamp analysis of transfected CHO cell lines expressing TRPV3.

[0231] Mouse TRPV3 and rat TRPV1 cDNA are subcloned into pcDNA5 (Invitrogen) and transfected into CHO-K1/FRT cells using Fugene 6 (Roche). The transfected cells are selected by growth in MEM medium containing 200 µg/mL hygromycin (Gibco BRL). Populations are frozen at early passages and these stocks are used for further studies. Stable clones that express the mRNAs are identified by Northern blot analysis as well as Southern blotting to confirm integration site. Long-term cultures are subsequently maintained at 33°C.

[0232] TRPV3 expressing CHO cells are assayed electrophysiologically using whole cell voltage clamped techniques. Currents are recorded via pCLAMP8 suite of software via an Axopatch 200A and filtered at 5 kHz. Series-resistance compensation for all experiments is 80% using 2-5 MΩ resistance, fire-polished pipettes. Unless stated, the holding potential for most experiments is -60 mV, apart from the current-voltage relationship studies (2 second ramp from -100 to +80 mV). Cells are normally bathed in a medium containing (mM): NaCl, 140; KCl, 5; Glucose, 10; HEPES, 10; CaCl₂, 2; MgCl₂ 1; titrated to pH 7.4 with NaOH, apart from the monovalent permeability studies, when NaCl is replaced by equimolar KCl or CsCl with the omission of KCl, 5 mM. For the divalent permeability studies, the solutions either contain 1 mM Ca²⁺ or Mg²⁺ and (mM) NaCl, 100; Glucose, 10; Hepes, 10; sucrose, 80 or 30 mM test ion, in the above solution minus sucrose. The experiments in calcium free media have no added CaCl₂ with the addition of 100 µM EGTA. Pipette solution is always (mM) CsCl, 140; CaCl₂, 1; EGTA, 10; HEPES, 10; MgATP, 2; titrated to pH7.4 with CsOH. For the permeability, ratios for the monovalent cations relative to Na (P_X/P_{Na}) are calculated as follows:

$$P_X/P_{Na} = E_{\text{shift}} = \{RT/F\} \log (P_X/P_{Na} [X]_O / [Na]_O)$$

where F is Faraday's constant, R is the universal gas constant, and T is absolute temperature. For the divalent ions, P_{Ca} or P_{Mg}/P_{Na} is calculated as follows:

$$E_{\text{shift}} = \{RT/F\} \log \{ [Na]_O + 4B' [X]_O (2) \} / \{ [Na]_O + 4B' [X]_O (1) \}$$

where $B' = P'_X/P_{Na}$ and $P'_X = P_X/(1 + e^{EF/RT})$ and $[X]_O (1)$ and $[X]_O (2)$ refer to the two different concentrations of the divalent ion tested.

[0233] The results from transfected cells assayed electrophysiologically via whole cell voltage clamped techniques are described below. Capsaicin (1 μ M), an activator of TRPV1, does not evoke a response in TRPV3-expressing cells. Similarly no current responses are seen when TRPV3-expressing cells are challenged with a hypo-osmotic solution containing 70 mM NaCl or with low pH (5.4). However, raising the temperature of superperfused external solution from room temperature to 45°C evokes currents in TRPV3 expressing cells. Analysis of currents evoked by temperature ramps from ~15°C to ~48°C (see Figure 3A) shows that little current is elicited until temperatures rise above ~33°C and that the current continues to increase in the noxious temperature range (>42°C). With these findings, TRPV3-expressing cells are subsequently maintained at 33°C to avoid constitutive activation. The current amplitude is influenced by the presence or absence of Ca^{2+} in the external medium, with reduced current amplitudes in the presence of 2 mM Ca^{2+} after a prior challenge in Ca^{2+} -free solution (see Figure 3B). This finding is reminiscent of the channel properties of TRPV5 and TRPV6 (see Nilius et al., *J. Physiol.*, 527:239-248 (2000)). As shown in Figure 3C, the heat evoked current in TRPV3-expressing CHO cells increases exponentially at temperatures above 35°C with an e-fold increase per $5.29 \pm 0.35^\circ\text{C}$ ($n=12$), corresponding to a mean Q_{10} of 6.62. This temperature dependence is considerably greater than that seen for most ion channel currents, which typically have Q_{10} values in the range 1.5-2.0, but is less than the values noted for TRPV1 (VR1, $Q_{10} = 17.8$) (see Vyklicky et al., *J. Physiol.*, 517:181-192 (1999)). In some cells it is difficult to see a sharp threshold temperature. However, measurable temperature dependent currents below 30°C show an e-fold increase for a $22.72 \pm 3.31^\circ\text{C}$ ($n=12$) increase in temperature ($Q_{10} = 1.69$).

[0234] The elevated temperature evoked currents, in TRPV3-expressing cells, shows a pronounced outward rectification (see Figure 3D) with a reversal potential in the standard recording solution of -1.22 ± 1 mV. Reducing the NaCl in the external solution to 70 mM (from 140 mM) shifts the reversal potential by -19mV as expected for a cation selective conductance (shift = -17.5 mV). Differences in reversal potentials are also used to determine the ionic selectivity of TRPV3 channels. In simplified external solutions, the reversal potentials of the heat activated currents are very similar when NaCl ($E_{\text{rev}} = -1.22 \pm 1.08$ mV, $n=5$) is replaced with either KCl ($E_{\text{rev}} = -0.40 \pm 0.77$ mV, $n=6$) or CsCl ($E_{\text{rev}} = -1.14 \pm 0.53$ mV, $n=6$), which yields relative permeability ratios $P_{\text{K}}/P_{\text{Na}}$ and $P_{\text{Cs}}/P_{\text{Na}}$ close to 1 (see Funayama et al., *Brain Res. Mol. Brain Res.*, 43:259-266 (1996)). The relative

permeability of Ca^{2+} and Mg^{2+} are estimated from the shift in reversal potentials when their concentrations are raised from 1 mM to 30 mM in a 100 mM NaCl solution containing the divalent cation under investigation. The reversal potential shifts (from -9.1 ± 1.40 mV to $+11.29 \pm 0.38$ mV for Ca^{2+} and from -8.41 ± 0.50 mV to $+10.34 \pm 2.38$ mV for Mg^{2+})

5 correspond to $P_{\text{Ca}}/P_{\text{Na}} = 2.57$ and $P_{\text{Mg}}/P_{\text{Na}} = 2.18$. These data show that TRPV3 is a non-selective cation channel that discriminates poorly between the tested monovalent cations and has significant divalent cation permeability.

[0235] Heat activation of TRPV3 shows a marked sensitization with repeated heat stimulation. This is studied at a steady membrane potential of -60 mV and with voltage
10 ramps. The first response to a step increase from room temperature to $\sim 48^\circ\text{C}$ is often very small, but the current response grew with repeated heat steps (see Figure 4A). Sensitization to heat has also been observed for TRPV1 and TRPV2 (see Caterina et al., *supra* and Jordt et al., *Cell*, 108:421-430 (2002)). Application of voltage ramps shows that sensitization is associated with an increase in outward rectification (see Figure 4B). A protocol of repeated
15 temperature challenges is used to investigate if antagonists of TRPV1 (VR1) are inhibitors of TRPV3. Under normal conditions, a heat challenge delivered 2 minutes after 4-5 sensitizing heat steps evokes a current that is 1.57 ± 0.25 ($n=4$) times the amplitude of the preceding response (see Figure 4C). Application of $10 \mu\text{M}$ capsazepine, a competitive capsaicin antagonist at TRPV1, for 2 minutes prior to the test heat challenge does not reduce the
20 current amplitude (2.31 ± 0.36 times the amplitude of the preceding response, $n=4$). In contrast, a similar exposure to $1 \mu\text{M}$ ruthenium red, a non-competitive inhibitor of other TRPV channels, reduces the relative amplitude of the heat response to 0.34 ± 0.03 , $n=5$ (see Figure 4D). Taken together, these results indicate that TRPV3 is a cation permeable channel activated by warm and hot temperatures and has channel properties reminiscent of other
25 TRPV channels.

EXAMPLE 4

Gene Expression Analysis of TRPV3 in the Rat Chung Model

[0236] These studies discussed below measure relative levels of RNA expression for TRPV3 in the Chung neuropathic pain model using RT-PCR.

A. Spinal nerve ligation (Chung) model

[0237] This model is established according to the methods described by Kim and Chung, *supra*, 1992. Rats are anesthetized and placed into a prone position and an incision made to the left of the spine at the L4-S2 level. A deep dissection through the paraspinal muscles and separation of the muscles from the spinal processes at the L4-S2 level will reveal part of the sciatic nerve as it branches to form the L4, L5 and L6 spinal nerves. The L6 transverse process is carefully removed with a small rongeur enabling visualization of these spinal nerves. The L5 spinal nerve is isolated and tightly ligated with 7-0 silk suture. The wound is closed with a single muscle suture (6-0 silk) and one or two skin closure clips and dusted with antibiotic powder. In sham animals the L5 nerve is exposed as before but not ligated and the wound closed as before.

[0238] Male Wistar rats (120-140 g) are used for each procedure. Mechanical hyperalgesia is assessed by measuring paw withdrawal thresholds of both hindpaws to an increasing pressure stimulus using an Analgesymeter (Ugo-Basile, Milan). Mechanical allodynia is assessed by measuring withdrawal thresholds to non-noxious mechanical stimuli applied with von Frey hairs to the plantar surface of both hindpaws. Thermal hyperalgesia is assessed by measuring withdrawal latencies to a noxious thermal stimulus applied to the underside of each hindpaw. With all models, mechanical hyperalgesia and allodynia and thermal hyperalgesia develop within 1-3 days following surgery and persist for at least 50 days. Drugs may be applied before and after surgery to assess their effect on the development of hyperalgesia, or approximately 14 days following surgery to determine their ability to reverse established hyperalgesia.

B. RT-PCR mRNA analysis

[0239] One microgram of total RNA samples from the Chung model (L4 and L5 DRG) and sham-operated animals are used for first-strand cDNA synthesis using 50 pmol of oligo (dt) 24 primer in a 20 µL total reaction with 200 units Superscript II (LTI). The cDNA is then diluted to 100 µL with Tris-EDTA buffer (10 mM TrisCl, pH 8.0 and 1 mM EDTA). Three µL of the diluted cDNA is used to amplify the message for TRPV3 with gene-specific primers (sequences in 5' to 3' orientation: TRPV3 forward primer, CTCATGCACAAGCTGACAGCCT (SEQ ID NO: 79); TRPV3 reverse primer, AGGCCTCTTCCGTGTACTCAGCGTTG (SEQ ID NO: 80)) in a 15 µL PCR reaction

using NotStart Taq DNA polymerase (Qiagen) for 25-38 cycles. Neuropeptide Y (NPY) is used as positive control.

[0240] For normalization 1 μ L of the diluted cDNA is used to amplify actin using the following primers:

5 5' actin primer: ATC TGG CAC CAC ACC TTC TAC AA (SEQ ID NO: 81)

3' actin primer: GCC AGC CAG GTC CAG ACG CA (SEQ ID NO: 82)

[0241] A portion of the samples are then analyzed on a 4-20 TBE Criterion polyacrylamide gel (BioRad), stained with SYBR GREEN I (Molecular Probes) and visualized on a Phosphorimager.

10 [0242] Figure 1A shows the average fold regulation of TRPV3 (VRLx) in L4 and L5 DRG neurons from the Chung model from three independent experiments. As shown in Figure 1A the positive control, NPY and TRPV3 message are elevated in the injured DRG relative to sham and non-ligated DRGs.

EXAMPLE 5

15 Identification of TRPV4

[0243] Primers are designed to amplify distinct regions of the candidate genes that had been identified through the computer model. Based on the human sequence obtained, PCR primers are designed to also amplify the mouse homologue of TRPV4 (mTRPV4) (TRPV4 forward: CTCATGCACAAGCTGACAGCCT (SEQ ID NO: 83); TRPV4 reverse: 20 AGGCCTCTTCCGTGTACTCAGCGTTG (SEQ ID NO: 84)). These PCR products are subsequently sequenced and the mouse EST database is searched using these sequences. One EST clone (ID No. AI510567) is identified and obtained from the IMAGE consortium. The EST is further characterized and found to contain a ~2.4 kb insert which is sequenced. Primers are designed from this sequence and used to obtain the full length cDNA using the 25 RACE protocol (Clontech). Both 5' and 3' RACE products are obtained and sequenced. This approach results in the amplification of the full length cDNA of mTRPV4 from mouse kidney and DRG cDNA using primers designed from the very 5' and 3' end of the RACE products. All primers utilized in the characterization of mTRPV4 are shown in Table 2. A novel full length cDNA of ~3.2 kb is identified, which includes an open-reading frame of 30 ~2.5 kb, a 5' UTR consisting of ~145 bp and a 3' UTR encompassing ~400-500 nucleotides. The gene encodes a 3.4 kb transcript that contains three ankryin-repeat regions and TM6

domains. The protein sequence includes ~1000 amino acids and is set forth in SEQ ID NO: 14. Clustal W alignments to the rat VR (GenBank Accession No. AF029310) reveals 34% identity and 64% similarity to VR1 in the region spanning the Ank2 through the TM4 region.

5

Table 2: TRPV4 Primers

		SEQ ID NO:
Primers used for RACE		
3' RACE	CCCTGGGCTGGGCGAACATGCTCTA	85
VR3RACE5'	CTTGGCAGCCATCATGAGAGGCGAA	86
Primers to amplify partial/full length TRPV4		
AP19	GCAGTGGTAACAACGCAGAG	87
AP20	AGGTCAGATCTGTGGCAGGT	88
AP21	CGTGAGGTGACAGATGAGGA	89
AP32	CCAGTATGGCAGATCCTGGT	90
AP25	ATGGCAGATCCTGGTGATG	91
		92
	<u>AP26 CCCAGGCACTACTGAGGACT</u>	93
		94
	<u>AP27 AGGGCTACGCTCCCAAGT</u>	95
	<u>AP28 GTGCTGGCTTAGGTGACTCC</u>	
AP22	TGAACTTGCGAGACAGATGC	

[0244] A combination of RT-PCR and Northern blot analyses are utilized to characterize expression of TRPV4. Total RNA is prepared from adult mouse kidney, newborn DRG and adult trigeminal tissue. RT-PCR is carried out using cDNA prepared from these three mouse tissues and primers within the ankyrin and the TM domain of mTRPV4. The expected 403 bp product is observed in all three tissues. This PCR product also serves as a probe on Northern blots (Clontech MTN blots). The expected 3.4 kb transcript is observed in kidney and other tissues.

[0245] The genomic structure of hTRPV4 is predicted from the high throughput genomic sequence database (GenBank Accession No. AC007834). HVR3 encompasses ~17 exons. A comparison of the amino acid sequence of the rat VR1 sequence (GenBank Accession No. AF029310) and the mouse VR3 protein reveals 34% identity and 64% similarity in the sequence spanning the ankyrin 2 region and the TM4 domain. The nucleotide and amino acid sequences of hTRPV4 are shown in SEQ ID NO: 16 and SEQ ID NO: 17, respectively.

EXAMPLE 6

Gene Expression Analysis of TRPV4 in the Rat Chung Model

[0246] These studies discussed below measure relative levels of RNA expression for TRPV4 in the Chung neuropathic pain model using RT-PCR.

5 ***A. Spinal nerve ligation (Chung) model***

[0247] This model is established according to the methods described by Kim and Chung, *supra*, and is described in Example 4.

B. RT-PCR mRNA analysis

[0248] One microgram of total RNA samples from the Chung model (L4 and L5
10 DRG) and sham-operated animals are used for first-strand cDNA synthesis using 50 pmol of oligo (dt) 24 primer in a 20 µL total reaction with 200 units Superscript II (LTI). The cDNA is then diluted to 100 µL with Tris-EDTA buffer (10 mM TrisCl, pH 8.0 and 1 mM EDTA). Three µL of the diluted cDNA is used to amplify the message for TRPV4 with gene-specific primers (Sequences in 5' to 3' orientation: TRPV4 forward primer, 99
15 TGAGGATGACATAGGTGATGAG 120 (SEQ ID NO: 96), TRPV4 reverse primer, 255 CCAAGGACAAAAAGGACTGC 236 (SEQ ID NO: 97)) in a 15 µL PCR reaction using NotStart Taq DNA polymerase (Qiagen) for 25-38 cycles. NPY is used as positive control:

[0249] For normalization 1 µL of the diluted cDNA is used to amplify actin using the following primers:

20 5'actin primer: ATC TGG CAC CAC ACC TTC TAC AA (SEQ ID NO: 81)

 3'actin primer: GCC AGC CAG GTC CAG ACG CA (SEQ ID NO: 82)

[0250] A portion of the samples are then analyzed on a 4-20 TBE Criterion polyacrylamide gel (BioRad), stained with SYBR GREEN I (Molecular Probes) and visualized on a Phosphorimager.

25 [0251] First-strand cDNA from the Chung model (50 days post-ligation) is normalized using a house-keeping gene; beta-actin. Figures 1A and 1B shows the expression of TRPV4 and NPY in the Chung Model (50- and 28-day post-ligation, respectively). The positive control, NPY and TRPV4 message are elevated in the injured DRG relative to sham and non-ligated DRGs. Accordingly, TRPV4 serves as a target for
30 neuropathic pain.

EXAMPLE 7**Identification of VR TRPM8**

[0252] To identify novel TRP channels, genomic DNA databases are searched by constructing a HMM from the known TRP protein sequences of different mammalian species. With this model, the 6-frame translation of all available human sequences is queried and identifies multiple novel putative exons with similarity to the TM4 and TM6 domains of VR1. A fragment of the mouse homologue of one novel TRP channel is amplified by RT-PCR from mouse DRG RNA. Full-length sequence of this gene is derived from a combination of exon-prediction software, PCR and RACE amplification from newborn mouse DRGs.

[0253] For PCR cloning, primers 163f (5'-CAAGTTTGTCCGCCTCTTTC (SEQ ID NO: 98)) and 164r (5'-AACTGTCTGGAGCTGGCAGT (SEQ ID NO: 99)) are designed from the HMM sequences for TRPM8 as a result of blast hits and used to amplify a 699-nucleotide fragment of TRPM8 from newborn DRG cDNA. From this initial sequence and exon prediction programs, RACE PCR (Clontech) is used to obtain the 5' and 3' ends of TRPM8 from mouse newborn DRG cDNA following the manufacturer's protocol. Primers used in these experiments are shown in Table 3.

Table 3: Primers to Amplify Mouse TRPM8 cDNA

		SEQ ID NO:
Putative trp candidate		
2KMHMR5R44-MOD CELERA HUMAN CONTIG		
FOR MOUSE:		
Probes designed for <i>in situ</i> hyb analysis		
AP163F	CAAGTTTGTCCGCCTCTTTC	100
AP164R	ACTGCCAGCTCCAGACAGTT	101
Rapid amplification of cDNA ends (RACE)		
5' RACE primers		
5' RACE (nested)	ccttcgatgtgctggctctgggcataa	102
5' RACE	CCTTGCCCTTTCTTCCCCAGAGTCTCAA	103
AP220 5' RACE	GCAAAGTTTTTGGCTCCACCCGTCA	104
AP2215' RACE (nested)	GCCAGTGCTGGGTCAGCAGTTCGTA	105
3' RACE primers		
3' RACE I	TTCAGGAGGTCATGTTCACGGCTCTCA	106
3' RACE I (nested)	GTACCGGAACCTGCAGATCGCCAAGA	107
AP218 3'RACE TRPXII	GCAAGATCCCTTGTGTGGTGGTGGGA	108
AP219 3' (nested)	CAGCCTGGTGGAGGTGGAGGATGTT	109
3' RACE #3	CGGAACCTGCAGATCGCCAAGAACT	110
3' RACE primer in TM5 region of TRPM8		
AP225	GCGTGGCCAGACAGGGGATCCTAAG	111
3' REVERSE primer in TM5 region of TRPM8		
AP226	CCACACAGCAAAGAGGAACA	112
To amplify longer piece of mouse TRPM8		
216F	GGAGCCGCAGAAATGGTACT	113
Primers used for Northern probe		
<u>Amplifies around 1.2 kB band</u>		
AP258	TCTCATTGGCCTCATTTCTG	114
AP247	ATATGAGACCCGAGCAGTGG	115

[0254] The protein TRPM8, has been named following the nomenclature suggested in Clapham et al., *Cell*, 108:595-598 (2001). Several human ESTs, many of which have been isolated from various cancer tissues, contain fragments of TRPM8 (Genbank GI Nos. 8750489, 9149390, 9335992 and 2223353).

[0255] Translation of the nucleotide sequence of TRPM8 predicts a protein composed of 1104 amino acid residues (see SEQ ID NO: 8). The overall sequence of mouse

TRPM8 is 93% identical to that of the human gene (see Figure 6A). Its closest relative is TRPM2 (42% identity) (see Figures 6A and 6B). TRPM8 belongs to the "long" or Melastatin subfamily of TRP channels, a group of TRPs characterized by their lack of ankyrin domains in the N-terminus. TRP channels are predicted to contain TM6 domains, although at least one is predicted to have seven membrane-spanning domains (see Nagamine et al., *Genomics*, 54:124-131 (1998)). A Kyte-Doolittle plot suggests the presence of eight distinct hydrophobic peaks in TRPM8 sequence, which could represent six to eight predicted transmembrane domains. Overall, the predicted transmembrane domains are within amino acids 695-1024 of TRPM8. Outside of this region, the only predicted secondary structures are coiled-coil domains present both in the N- and C-terminal portion of the protein (data not shown) (see Burkhard et al., *Trends Cell. Biol.*, 11:82-88 (2001)). Coiled-coil domains are implicated in oligomerization of GABA-B channels, and have been previously predicted in some TRP channels (see Funayama et al., *supra*; and Margeta-Mitrovic et al., *Neuron*, 27:97-106 (2000)).

EXAMPLE 8

Localization of TRPM8 expression

A. Northern blot analysis

[0256] Northern blots are made as followed: Total RNA are purified from mouse newborn and adult tissues using TRIzol LS (Invitrogen/Gibco Life technologies), followed by polyA⁺ purification with Oligotex (Qiagen) according to the manufacturer's protocols. Approximately 3 mg of sample are electrophoresed on 1% glyoxal gels, transferred and hybridized at high-stringency with a ³²P-labeled probe representing nucleotides 1410-1980 of the mouse full-length TRPM8 sequence. Commercial Northern blots (Clontech) are hybridized with the same TRPM8 probe. Blots are hybridized for 3 hours at 68°C in ExpressHyb hybridization solution (Clontech) and washed according to the manufacturer's high-stringency washing protocol and exposed to a phosphorimager screen for 1-3 days.

[0257] The results from this analysis are described below. No TRPM8 expression is detected using commercial Northern blots. Blots from newborn and adult mice are used that include tissues relevant for somatic sensation, including DRG, spinal cord and different

sources of skin. One mRNA species of approximately 6.3 kb is present predominantly in DRGs.

B. *In situ* hybridization

[0258] For *in situ* hybridizations, newborn and adult tissues are dissected, fixed in 4% paraformaldehyde in PBS, cryoprotected and frozen in liquid nitrogen in OCT mounting medium. Cryostat sections (10 μ m) are processed and hybridized with a digoxigenin cRNA probe generated by *in vitro* transcription (Roche Biochemicals). The mouse TRPM8 mRNA-specific antisense riboprobe corresponds to nucleotides 1410-1980 of the mTRPM8 sequence. Fluorescence detection and double-labeling experiments are carried out with the tyramide signal amplification kit (TSA; NEN) essentially as previously described (see Dong et al., *Cell*, 106:619-632 (2001)).

[0259] Digoxigenin-labeled probes show specific expression in DRG and trigeminal ganglia (cranial sensory neurons innervating the mouth and jaw) in newborn and adult mouse, but not in day 13 embryos. TRPM8 expression is restricted to approximately 5-10% of adult DRG neurons. The average size of the neurons positive for TRPM8 is 18 ± 3.1 μ m (mean \pm standard deviation, n=69), and can be classified as small-diameter c-fiber-containing neurons, which in mouse are defined as smaller than 25 μ m. TRPM8 is not expressed in heavily-myelinated neurons marked by Neurofilament (NF) antibodies, which correlates well with TRPM8 expression in small-sized neurons. TRPM8⁺ neurons thus appear to belong to a subset of nociceptive or thermoceptive neurons that express trkA, an NGF receptor, during development (see Huang and Reichardt, *Ann. Rev. Neurosci.*, 24:677-736 (2001)). In the absence of NGF or trkA, DRG neurons that normally express this receptor die through apoptosis during embryonic development (Huang and Reichardt, *supra*). To prove that TRPM8 is expressed in trkA-dependent neurons, TRPM8 expression is evaluated in DRGs from newborn trkA-null mice. The expression of TRPM8 is completely abolished in the mutant ganglia. In addition, TRPM8 is not co-expressed with VR1, which marks a class of nociceptors that respond to capsaicin and noxious heat. This observation is confirmed by the lack of TRPM8 co-expression with either CGRP or IB4, two well-characterized antigenic markers found on nociceptive neurons (see Snider and McMahon, *Neuron*, 20:629-632 (1998); Tominaga et al., *Neuron*, 21:531-543 (1998)). This data strongly indicates that TRPM8 is expressed in a subpopulation of

thermoceptive/nociceptive neurons distinct from the well-characterized heat and pain sensing neurons marked by VR1, CGRP or IB4.

[0260] Following *in situ* hybridization, immunofluorescence is performed with anti-CGRP (1:100; Biogenesis), IB-4 (10 µg/mL; Sigma), anti-VR1 (1/2000; Abcam), anti-NF150 (1/1000; Chemicon) and detected with FITC or CY3 (10 µg/mL; Jackson Immunoresearch). Although all panels shown in these studies demonstrate lack of co-expression, this is not due to technical issues since additional probes/antibodies are used as controls to ensure our double-labeling protocol with the TRPM8 *in situ* probe is working.

EXAMPLE 9

Activation of TRPM8 Protein by Cold and Menthol

A. Effect of heat, capsaicin, cold and menthol upon intracellular calcium

[0261] Given the similarity of TRPM8 protein to TRPV family members and its unique expression pattern, the effects of heat, capsaicin, cold and menthol in mediating calcium influx are examined using transfected CHO-K1/FRT cells expressing TRPM8 protein and a fluorescent calcium imaging method as described in detail below.

[0262] To generate mouse TRPM8-expressing CHO cell lines, mouse TRPM8 cDNA are subcloned in pcDNA5 (Invitrogen), transfected into CHO-K1/FRT cells using Fugene 6 (Roche). The transfected cells are selected by growth in MEM medium containing 200 µg/µL⁻¹ hygromycin (Gibco BRL). Populations are frozen at early passage numbers and these stocks are used for further studies. Stable clones that express the mRNAs are identified by Northern blot analysis as well as Southern blotting to confirm integration site (not shown). CHO cells do not express an endogenous TRPM8 isoform and therefore serve as a control along with a cell line stably transfected with a VR1-expressing plasmid.

[0263] Calcium imaging experiments are performed essentially as previously described (see Savidge et al., *Neuroscience*, 102:177-184 (2001)). Briefly, cells are plated on glass coverslips and loaded with Fura-2 acetoxymethyl ester (2.5-5 mM) and incubated for 30-60 minutes at room temperature in 1.5 mM of pluronic acid (Molecular Probes, Eugene, OR) in a HEPES-buffered saline (2 mM Ca²⁺). Coverslips are placed in a laminar flow perfusion chamber (Warner Instrument Corp.) and constantly perfused with HEPES-buffered saline (2 mM Ca²⁺) via a local perfusion pipette through which buffer and chilled

solutions are also applied. Chilled stimulations consist of a linear decrease ($\sim 1-1.5^{\circ}\text{C sec}^{-1}$) in perfusate temperature from 33°C to 10°C . Perfusate temperature is controlled by a regulated Peltier device and is monitored in the cell chamber by a miniature thermocouple. Alternatively, cells are plated on 24-well tissue culture plates, loaded with Fura-2 and application of solutions is performed with a 3 cc syringe over a period of 10 seconds. Images of Fura-2 loaded cells with the excitation wavelength alternating between 340 and 380 nm are captured with a cooled CCD camera. Following subtraction of background fluorescence, the ratio of fluorescence intensity at the two wavelengths is calculated. Ratio levels in groups of 20-40 individual cells are analyzed using MetaFluor (Universal Imaging Corporation). All graphs are averaged responses from groups of 20-30 individual cells from representative single experiments. All experiments are repeated on three separate occasions and similar results obtained. Hanks balanced salt solution (HBSS), phosphate buffered saline (PBS) and all cell culture reagents are obtained from Gibco BRL. Ruthenium red, capsaicin and menthol are obtained from Sigma.

[0264] The results of the above calcium imaging experiments are described below. Capsaicin ($10\text{ }\mu\text{M}$), an activator of VR1, does not evoke a response in TRPM8 expressing cells. Neither hypo-osmotic solutions, known to generate Ca^{2+} responses in TRPV3-expressing cells, or hypertonic buffer elicit a response in TRPM8 expressing cell lines (see Liedtke et al., *supra*; and Strotmann et al., *supra*). An increase in temperature ($25-50^{\circ}\text{C}$), a potent stimulus for VR1, also does not alter intracellular calcium levels. However, when the temperature is lowered from 25°C to 15°C , an increase in intracellular calcium is observed in TRPM8 expressing cells (Figures 7A and 8A). This response is not observed in non-transfected CHO cells or the VR1-expressing cell line (Figures 7A and 8A). Addition of a 10°C stimulus also evokes an influx of Ca^{2+} . This response is dependent on Ca^{2+} in the buffer, because removal of extracellular calcium suppresses the temperature response (Figures 7A and 8A). The dependence on outside calcium is indicative of a cation-permeable channel localized at the plasma membrane. A potent blocker of the heat response for VR1, ruthenium red (at $5\text{ }\mu\text{M}$), does not suppress the temperature response.

[0265] Since TRPM8 responds to a decrease in temperature, additional experiments are carried out to investigate the temperature threshold at which intracellular calcium ($[\text{Ca}^{2+}]_i$) begins to rise in TRPM8 expressing cells. Cells are incubated at 35°C (normal skin temperature) for several minutes followed by a decrease in temperature to

13°C. The temperature response in mouse TRPM8-CHO cells shows a threshold of 22-25°C at which $[Ca^{2+}]_i$ starts to increase (Figure 7B), followed by a marked increase when the temperature of the buffer reached ~15°C. These experiments indicate that at physiological relevant temperatures, the upper activation threshold for TRPM8 is ~23°C (Figure 7C).

5 [0266] Menthol, a compound commonly used for its cooling properties, is tested as a stimulus on TRPM8 expressing CHO cells. Non-transfected CHO cells are completely insensitive to menthol (tested up to 1 mM) (Figure 7D). However, upon treatment of TRPM8 cells (incubated at 25°C), intracellular fluorescence increases significantly within seconds in response to menthol concentrations of 10 and 100 µM (Figure 7D). Additionally,
10 as with the temperature stimulus, depletion of calcium from the extracellular buffer suppresses the calcium response (Figure 7D). The effect that menthol has at different temperatures is also examined. Incubation of TRPM8 expressing cells at 33°C, reveals that 10 µM menthol does not induce a calcium response as observed at 25°C, but upon lowering the temperature to 30°C, intracellular calcium levels increases (Figure 7E). Menthol thus
15 appears to mimic the effect of lowering the temperature on TRPM8 expressing cells.

B. Effect of cold and menthol upon conductance

[0267] To investigate the membrane responses to cold and menthol, voltage clamp experiments are carried out on TRPM8 expressing cells which are prepared as described above.

20 [0268] Cells are plated onto poly-D-lysine coated cover-slips for recording purposes and recordings undertaken 18-24 hours later. Experiments are carried out at room temperature using whole-cell voltage clamp technique, with an Axopatch 2B amplifier, filtered at 5 kHz and pClamp suite of software (Axon Instruments). Series resistant compensation is 80% for all experiments, using 2-5 MΩ fire-polished pipettes. Recording
25 solutions are as follows; pipette solution for all experiments is (mM) CsCl, 140; CaCl₂, 1; EGTA, 10; HEPES, 10; MgATP, 2; titrated to pH 7.4 with CsOH. For menthol and cold activated currents the bath solution is (mM): NaCl, 140; KCl, 5; Glucose, 10; HEPES, 10; CaCl₂, 2; MgCl₂, 1; titrated to pH 7.4 with NaOH. Current-voltage relationships are used to evaluate reversal potentials with voltage ramps from -100 to +60 mV (2 second duration).
30 For the permeability studies for the monovalent ions the NaCl in a simplified bath solution (mM): NaCl, 140; Glucose, 10; HEPES, 10; CaCl₂, 2; MgCl₂, 1, is substituted by either

equimolar CsCl or KCl (titrated with CsOH or KOH). For calcium permeability estimates, the bath solutions contains (mM) NaCl, 100; Glucose, 10 mM; Hepes, 10 mM (titrated with NaOH) plus 1 or 30 mM CaCl₂. Osmolarity of solutions are adjusted by addition of sucrose. Permeability ratios for the monovalent cations to Na (P_X/P_{Na}) are calculated as follows:

$$P_X/P_{Na} = E_{\text{shift}} = \{RT/F\} \log (P_X/P_{Na} [X]_O / [Na]_O)$$

where F is Faraday's constant, R is the universal gas constant and T is absolute temperature. For measurements of calcium permeability P_{Ca}/P_{Na} is calculated as follows:

$$E_{\text{shift}} = \{RT/F\} \log \{ [Na]_O + 4B' [Ca]_{O(2)} \} / \{ [Na]_O + 4B' [Ca]_{O(1)} \}$$

where $B' = P'_{Ca}/P_{Na}$ and $P'_{Ca} = P_{Ca} / (1 + e^{EF/RT})$ and $[Ca]_{O(1)}$ and $[Ca]_{O(2)}$ refer to the

two different calcium concentrations. Local perfusion of menthol is via a TC²bip temperature controller. A Marlow temperature controller is used for the cooling ramps.

[0269] The results of the voltage clamp studies carried out on TRPM8 expressing cells are described below. Temperature ramps from 35°C to 7-13°C evoke inward currents at a holding potential of -60 mV and outward currents at +40 or +60 mV. Currents increase in amplitude as the temperature is lowered and usually show some degree of desensitization at the coldest temperatures tested <10°C (Figure 9A). The temperature threshold for current activation shows no dependence on membrane potential and individual cells activated at temperatures between 19°C and 25°C, with a mean threshold of $21.79 \pm 0.64^\circ\text{C}$ (n=5). Analysis of the current-voltage relationships of the response to a cold stimulus with CsCl filled recording pipettes and a typical NaCl-based external solution reveals an outwardly rectifying current with a reversal potential (E_{rev}) close to 0 mV which is typical of a non-selective cation channel (Figure 9B).

[0270] Application of menthol evokes rapidly activating currents in TRPM8 expressing, but not in non-transfected CHO cells at temperatures above the threshold for cold activation (>23°C, Figure 10A). The menthol activated current shows pronounced outward rectification (Figure 10B) with an E_{rev} of -9.28 ± 0.75 mV (n=12) that is similar to the E_{rev} for the cold-activated current under the same ionic conditions. These currents could be inactivated by raising the temperature (see Figure 10A) suggesting that menthol shifts the threshold for activation to higher temperatures, which agrees with the calcium imaging experiments. To test this idea further, concentration-response curves for menthol-evoked currents at two temperatures (22°C and 35°C) are obtained using positive membrane potentials to increase the size of the currents (Figures 11A and 11B). The concentration-

response relationship is shifted to the left at the lower temperature with a marked increase in the maximum amplitudes (Figures 11A and 11B). Changes in E_{rev} are used to determine the ion selectivity of the menthol activated current. Isotonic replacement of the NaCl in the solution with KCl or CsCl, causes small positive shifts in E_{rev} indicating that the TRPM8 channel discriminates poorly between these cations (data not shown). From the changes in E_{rev} measured on individual cells (external NaCl to KCl gives a shift of $+7.38 \pm 1.43$ mV, $n=7$; NaCl to CsCl gives a shift of $+9.09 \pm 0.36$ mV, $n=5$) a permeability sequence of $Cs > K > Na$ is calculated with $P_{Cs}/P_{Na} = 1.43$ and $P_K/P_{Na} = 1.34$. Relative calcium permeability is calculated from the E_{rev} values measured with different external calcium concentrations. Increasing the external calcium from 1-30 mM, in the absence of external Mg^{2+} ions, shifts E_{rev} by $+11.67 \pm 1.20$ mV, which corresponds to $P_{Ca}/P_{Na} = 0.97$. Thus TRPM8 is permeable to the monovalent cations, Na, K and Cs as well as the divalent cation calcium.

[0271] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. An isolated TRPV3 nucleic acid molecule comprising a member selected from the group consisting of:

- a) a polynucleotide that encodes a mouse TRPV3 protein comprising amino acid residues 1-791 of SEQ ID NO: 2;
- b) a polynucleotide that encodes a mouse TRPV3 protein comprising amino acid residues 2-791 of SEQ ID NO: 2;
- c) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a mouse TRPV3 protein;
- d) a polynucleotide that encodes a human TRPV3 protein comprising amino acid residues 1-791 of SEQ ID NO 5;
- e) a polynucleotide that encodes a human TRPV3 protein comprising amino acid residues 2-791 of SEQ ID NO 5;
- f) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a human TRPV3 protein; and
- g) a polynucleotide that is complementary to a polynucleotide of a) through f).

2. The TRPV3 nucleic acid molecule of claim 1, wherein the nucleic acid molecule is a polydeoxyribonucleic acid (DNA).

3. The TRPV3 nucleic acid molecule of claim 1, wherein the nucleic acid molecule is a polyribonucleic acid (RNA).

4. The TRPV3 nucleic acid molecule of claim 1, wherein the nucleic acid molecule is a) or b) and comprises a first polynucleotide 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 3.

5. The TRPV3 nucleic acid molecule of claim 4, wherein the first polynucleotide is 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 65-2440 of SEQ ID NO: 1.

6. The TRPV3 nucleic acid molecule of claim 4, wherein the first polynucleotide is 90% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 65-2440 of SEQ ID NO: 1.

5 7. The TRPV3 nucleic acid molecule of claim 4, wherein the first polynucleotide comprises a nucleotide sequence as set forth in nucleotides 65-2440 of SEQ ID NO: 1.

8. The TRPV3 nucleic acid molecule of claim 1, wherein the nucleic acid molecule is d) or e) and comprises a first polynucleotide 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 6.

10 9. The TRPV3 nucleic acid molecule of claim 8, wherein the first polynucleotide is 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 57-2432 of SEQ ID NO: 4.

10 10. The TRPV3 nucleic acid molecule of claim 9, wherein the first polynucleotide is 90% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 57-2432 of SEQ ID NO: 4.

11. The TRPV3 nucleic acid molecule of claim 9, wherein the first polynucleotide comprises a nucleotide sequence as set forth in nucleotides 57-2432 of SEQ ID NO: 4.

20 12. The TRPV3 nucleic acid molecule of claim 1, wherein the nucleic acid molecule is c) or f) and the polypeptide comprises one or more functional domains selected from the group consisting of:

- 25
- a) an ankyrin domain;
 - b) a transmembrane region;
 - c) a pore loop region; and
 - d) a coiled-coil domain.

13. The TRPV3 nucleic acid molecule of claim 12, wherein the polypeptide comprises a pore loop region flanked by two transmembrane regions.

14. The TRPV3 nucleic acid molecule of claim 12, wherein the polypeptide comprises four ankyrin domains.

15. The TRPV3 nucleic acid molecule of claim 1, wherein the nucleic acid molecule further comprises a heterologous nucleic acid.

5 16. The TRPV3 nucleic acid molecule of claim 15, wherein the heterologous nucleic acid comprises a promoter operably linked to the TRPV3 polynucleotide.

17. The TRPV3 nucleic acid molecule of claim 15, wherein the heterologous nucleic acid comprises an expression vector.

10 18. A host cell that comprises a TRPV3 nucleic acid molecule of claim 15.

19. An isolated TRPV3 polypeptide comprising a member selected from the group consisting of:

- a) a mouse TRPV3 protein comprising amino acid residues 1-791 of SEQ ID NO: 2;
- 15 b) a mouse TRPV3 protein comprising amino acid residues 2-791 of SEQ ID NO: 2;
- c) one or more functional domains of a mouse TRPV3 protein;
- d) a human TRPV3 protein comprising amino acid residues 1-791 of SEQ ID NO 5;
- 20 e) a human TRPV3 protein comprising amino acid residues 2-791 of SEQ ID NO 5; and
- f) one or more functional domains of a human TRPV3 protein.

20. The TRPV3 polypeptide of claim 19, wherein the TRPV3 polypeptide is c) or f) and comprises one or more functional domains selected from the group consisting of:

25

- a) an ankyrin domain;
- b) a transmembrane region;
- c) a pore loop region; and

d) a coiled-coil domain.

21. The TRPV3 polypeptide of claim 20, wherein the polypeptide comprises a pore loop region flanked by two transmembrane regions.

5 22. The TRPV3 polypeptide of claim 20, wherein the polypeptide comprises four ankyrin domains.

23. An antibody that specifically binds to a TRPV3 polypeptide of claim 19.

24. A method for identifying an agent that modulates TRPV3-mediated cation passage through a membrane, the method comprising:

- 10 a) providing a membrane that comprises a TRPV3 polypeptide of claim 19;
- b) contacting the membrane with a candidate agent; and
- c) determining whether passage of one or more cations through the membrane is increased in the presence of the candidate agent
- 15 compared to passage in the absence of the candidate agent.

25. The method of claim 24, wherein the membrane comprises a cell and cation passage through the membrane is detected by measuring cation influx across the membrane into the cell.

20 26. The method of claim 25, wherein the cell comprises a promoter operably linked to a heterologous polynucleotide that encodes the TRPV3 polypeptide.

27. The method of claim 24, wherein cation passage through the membrane is detected by voltage clamping.

28. The method of claim 24, wherein cation passage through the membrane is detected by an ion sensitive dye or a membrane potential dye.

25 29. The method of claim 24, wherein the assay is conducted at a temperature of at least 33°C.

30. The method of claim 24, wherein the assay is conducted at a temperature of less than 52°C.

31. The method of claim 30, wherein the assay is conducted at a temperature of less than 43°C.

5 32. The method of claim 24, wherein the membrane is contacted with the candidate modulating agent in a well of a multiwell plate.

33. The method of claim 32, wherein the multiwell plate is a 96-, 384- or 1536-well plate.

10 34. The method of claim 24, wherein a candidate agent that reduces cation passage is further tested for ability to treat pain by administering the candidate agent to a test animal and determining whether the candidate agent decreases the test animal's response to a pain stimulus.

35. The method of claim 34, wherein the pain stimulus is exposure to a temperature above 33° C.

15 36. A method of reducing pain associated with TRPV3 activity, the method comprising administering to a subject suffering from pain an analgesically effective amount of a compound that reduces TRPV3-mediated cation passage through a membrane or reduces signal transduction from a TRPV3 polypeptide to a DRG neuron.

20 37. The method of claim 36, wherein the pain is associated with one or more of heat exposure, inflammation, or tissue damage.

38. The method of claim 36, wherein the compound is selected from the group consisting of:

- 25
- a) an antibody that specifically binds to a TRPV3 polypeptide;
 - b) an antisense polynucleotide, ribozyme, or an interfering RNA that reduces expression of a TRPV3 polypeptide; and
 - c) a chemical compound that reduces cation passage through a membrane that comprises a TRPV3 polypeptide.

39. The method of claim 38, wherein the chemical compound has a molecular weight of 1000 daltons or less.

40. A method for determining whether pain in a subject is mediated by TRPV3, the method comprising:

- 5 a) obtaining a sample from a region of the subject at which the pain is felt; and
- b) testing the sample to determine whether a TRPV3 polypeptide or TRPV3 polynucleotide is present in the sample.

10 41. The method of claim 40, wherein the presence of a TRPV3 polypeptide in the sample is detected by determining whether cation passage across membranes of cells in the sample is mediated by a TRPV3 polypeptide.

 42. The method of claim 41, wherein TRPV3 involvement in mediating cation passage across membranes of the cells is determined by detecting an increase in cation passage across membranes of the cells when assayed above 33°C compared to cation passage
15 when assayed below 33°C.

 43. The method of claim 40, wherein the presence of a TRPV3 polypeptide in the sample is detected by contacting the sample with a reagent that specifically binds to a TRPV3 polypeptide.

 44. The method of claim 43, wherein the reagent comprises an antibody.

20 45. The method of claim 40, wherein the presence of a TRPV3 polynucleotide in the sample is detected by contacting nucleic acids from the sample with a test polynucleotide that can hybridize to a TRPV3 polynucleotide.

 46. The method of claim 45, wherein the test polynucleotide comprises an oligonucleotide at least 10 nucleotides in length.

25 47. The method of claim 45, wherein the method comprises amplification of a TRPV3 polynucleotide, if present in the sample.

48. The method of claim 47, wherein the amplification comprises polymerase chain reaction or ligase chain reaction.

49. The method of claim 45, wherein the test polynucleotide is attached to a solid support.

50. The method of claim 49, wherein the solid support comprises a microchip.

51. An isolated TRPV4 nucleic acid molecule comprising a member selected from the group consisting of:

- a) a polynucleotide that encodes a mouse TRPV4 protein comprising amino acid residues 1-871 of SEQ ID NO: 14;
- b) a polynucleotide that encodes a mouse TRPV4 protein comprising amino acid residues 2-871 of SEQ ID NO: 14;
- c) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a mouse TRPV4 protein;
- d) a polynucleotide that encodes a human TRPV4 protein comprising amino acid residues 1-871 of SEQ ID NO 17;
- e) a polynucleotide that encodes a human TRPV4 protein comprising amino acid residues 2-871 of SEQ ID NO 17;
- f) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a human TRPV4 protein; and
- g) a polynucleotide that is complementary to a polynucleotide of a) through f).

52. The TRPV4 nucleic acid molecule of claim 51, wherein the nucleic acid molecule is a polydeoxyribonucleic acid (DNA).

53. The TRPV4 nucleic acid molecule of claim 51, wherein the nucleic acid molecule is a polyribonucleic acid (RNA).

54. The TRPV4 nucleic acid molecule of claim 51, wherein the nucleic acid molecule is a) or b) and comprises a first polynucleotide 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 15.

55. The TRPV4 nucleic acid molecule of claim 54, wherein the first
5 polynucleotide is 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 156-2771 of SEQ ID NO: 13.

56. The TRPV4 nucleic acid molecule of claim 54, wherein the first polynucleotide is 90% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 156-2771 of SEQ ID NO: 13.

10 57. The TRPV4 nucleic acid molecule of claim 56, wherein the first polynucleotide comprises a nucleotide sequence as set forth in nucleotides 156-2771 of SEQ ID NO: 13.

58. The TRPV4 nucleic acid molecule of claim 51, wherein the nucleic acid molecule is d) or e) and comprises a first polynucleotide 80% or more identical to a
15 second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 18.

59. The TRPV4 nucleic acid molecule of claim 58, wherein the first polynucleotide is 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 16.

60. The TRPV4 nucleic acid molecule of claim 58, wherein the first
20 polynucleotide is 90% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 16.

61. The TRPV4 nucleic acid molecule of claim 60, wherein the first polynucleotide comprises a nucleotide sequence as set forth in SEQ ID NO: 16.

62. The TRPV4 nucleic acid molecule of claim 51, wherein the nucleic acid
25 molecule is c) or f) and the polypeptide comprises one or more functional domains selected from the group consisting of:

a) an ankyrin domain;

- b) a transmembrane region;
- c) a pore loop region; and
- d) a coiled-coil domain.

63. The TRPV4 nucleic acid molecule of claim 62, wherein the polypeptide
5 comprises a pore loop region flanked by two transmembrane regions.

64. The TRPV4 nucleic acid molecule of claim 62, wherein the polypeptide
comprises three ankyrin domains.

65. The TRPV4 nucleic acid molecule of claim 51, wherein the nucleic acid
molecule further comprises a heterologous nucleic acid.

10 66. The TRPV4 nucleic acid molecule of claim 65, wherein the
heterologous nucleic acid comprises a promoter operably linked to the TRPV4
polynucleotide.

67. The TRPV4 nucleic acid molecule of claim 65, wherein the
heterologous nucleic acid comprises an expression vector.

15 68. A host cell that comprises a TRPV4 nucleic acid molecule of claim 65.

69. An isolated TRPV4 polypeptide comprising a member selected from the
group consisting of:

- a) a mouse TRPV4 protein comprising amino acid residues 1-871 of
SEQ ID NO: 14;
- 20 b) a mouse TRPV4 protein comprising amino acid residues 2-871 of
SEQ ID NO: 14;
- c) one or more functional domains of a mouse TRPV4 protein;
- d) a human TRPV4 protein comprising amino acid residues 1-871 of
SEQ ID NO 17;
- 25 e) a human TRPV4 protein comprising amino acid residues 2-871 of
SEQ ID NO 17; and
- f) one or more functional domains of a human TRPV4 protein.

70. The TRPV4 polypeptide of claim 69, wherein the polypeptide is c) or f) and comprises one or more functional domains selected from the group consisting of:

- a) an ankyrin domain;
- b) a transmembrane region;
- c) a pore loop region; and
- d) a coiled-coil domain.

71. The TRPV4 polypeptide of claim 70, wherein the polypeptide comprises a pore loop region flanked by two transmembrane regions.

72. The TRPV4 polypeptide of claim 70, wherein the polypeptide comprises three ankyrin domains.

73. An antibody that specifically binds to a TRPV4 polypeptide of claim 69.

74. A method for identifying an agent that modulates TRPV4-mediated cation passage through a membrane, the method comprising:

- a) providing a membrane that comprises a TRPV4 polypeptide of claim 69;
- b) contacting the membrane with a candidate agent; and
- c) determining whether passage of one or more cations through the membrane is increased in the presence of the candidate agent compared to passage in the absence of the candidate agent.

75. The method of claim 74, wherein the membrane comprises a cell and cation passage through the membrane is detected by measuring cation influx across the membrane into the cell.

76. The method of claim 75, wherein the cell comprises a promoter operably linked to a heterologous polynucleotide that encodes the TRPV4 polypeptide.

77. The method of claim 74, wherein cation passage through the membrane is detected by voltage clamping.

78. The method of claim 74, wherein cation passage through the membrane is detected by an ion sensitive dye or a membrane potential dye.

79. The method of claim 74, wherein the membrane is contacted with the candidate modulating agent in a well of a multiwell plate.

5 80. The method of claim 79, wherein the multiwell plate is a 96-, 384- or 1536-well plate.

 81. The method of claim 74, wherein a candidate agent that reduces cation passage is further tested for ability to treat pain by administering the candidate agent to a test animal and determining whether the candidate agent decreases the test animal's response to a
10 pain stimulus.

 82. The method of claim 81, wherein the pain is neuropathic pain.

 83. A method of reducing pain associated with TRPV4 activity, the method comprising administering to a subject suffering from pain an analgesically effective amount of a compound that reduces TRPV4-mediated cation passage through a membrane or reduces
15 signal transduction from a TRPV4 polypeptide to a DRG neuron.

 84. The method of claim 83, wherein the pain is neuropathic pain.

 85. The method of claim 83, wherein the compound is selected from the group consisting of:

- 20 a) an antibody that specifically binds to a TRPV4 polypeptide;
 b) an antisense polynucleotide, ribozyme, or an interfering RNA that reduces expression of a TRPV4 polypeptide; and
 c) a chemical compound that reduces cation passage through a membrane that comprises a TRPV4 polypeptide.

 86. The method of claim 85, wherein the chemical compound has a
25 molecular weight of 1000 daltons or less.

 87. A method for determining whether pain in a subject is mediated by TRPV4, the method comprising:

- a) obtaining a sample from a region of the subject at which the pain is felt; and
- b) testing the sample to determine whether a TRPV4 polypeptide or TRPV4 polynucleotide is present in the sample.

5 88. The method of claim 87, wherein the presence of a TRPV4 polypeptide in the sample is detected by determining whether cation passage across membranes of cells in the sample is mediated by a TRPV4 polypeptide.

 89. The method of claim 87, wherein the presence of a TRPV4 polypeptide in the sample is detected by contacting the sample with a reagent that specifically binds to a
10 TRPV4 polypeptide.

 90. The method of claim 89, wherein the reagent comprises an antibody.

 91. The method of claim 87, wherein the presence of a TRPV4 polynucleotide in the sample is detected by contacting nucleic acids from the sample with a test polynucleotide that can hybridize to a TRPV4 polynucleotide.

15 92. The method of claim 91, wherein the test polynucleotide comprises an oligonucleotide at least 10 nucleotides in length.

 93. The method of claim 91, wherein the method comprises amplification of a TRPV4 polynucleotide, if present in the sample.

 94. The method of claim 93, wherein the amplification comprises
20 polymerase chain reaction or ligase chain reaction.

 95. The method of claim 91, wherein the test polynucleotide is attached to a solid support.

 96. The method of claim 95, wherein the solid support comprises a microchip.

25 97. An isolated TRPM8 nucleic acid molecule comprising a member selected from the group consisting of:

- a) a polynucleotide that encodes a mouse TRPM8 protein comprising amino acid residues 1-1104 of SEQ ID NO: 8;
- b) a polynucleotide that encodes a mouse TRPM8 protein comprising amino acid residues 2-1104 of SEQ ID NO: 8;
- 5 c) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a mouse TRPM8 protein;
- d) a polynucleotide that encodes a human TRPM8 protein comprising amino acid residues 1-1268 of SEQ ID NO 11;
- e) a polynucleotide that encodes a human TRPM8 protein comprising amino acid residues 2-1268 of SEQ ID NO 11;
- 10 f) a polynucleotide that encodes a polypeptide that comprises one or more functional domains of a human TRPM8 protein; and
- g) a polynucleotide that is complementary to a polynucleotide of a) through f).

15 **98.** The TRPM8 nucleic acid molecule of claim 97, wherein the nucleic acid molecule is a polydeoxyribonucleic acid (DNA).

99. The TRPM8 nucleic acid molecule of claim 97, wherein the nucleic acid molecule is a polyribonucleic acid (RNA).

20 **100.** The TRPM8 nucleic acid molecule of claim 97, wherein the nucleic acid molecule is a) or b) and comprises a first polynucleotide 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 9.

101. The TRPM8 nucleic acid molecule of claim 100, wherein the first polynucleotide is 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 448-3762 of SEQ ID NO: 7.

25 **102.** The TRPM8 nucleic acid molecule of claim 100, wherein the first polynucleotide is 90% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 448-3762 of SEQ ID NO: 7.

103. The TRPM8 nucleic acid molecule of claim 102, wherein the first polynucleotide comprises a nucleotide sequence as set forth in nucleotides 448-3762 of SEQ ID NO: 7.

5 104. The TRPM8 nucleic acid molecule of claim 97, wherein the nucleic acid molecule is d) or e) and comprises a first polynucleotide 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in SEQ ID NO: 12.

105. The TRPM8 nucleic acid molecule of claim 104, wherein the first polynucleotide is 80% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 61-4821 of SEQ ID NO: 10.

10 106. The TRPM8 nucleic acid molecule of claim 104, wherein the first polynucleotide is 90% or more identical to a second polynucleotide having a nucleotide sequence as set forth in nucleotides 61-4821 of SEQ ID NO: 10.

15 107. The TRPM8 nucleic acid molecule of claim 106, wherein the first polynucleotide comprises a nucleotide sequence as set forth in nucleotides 61-4821 of SEQ ID NO: 10.

108. The TRPM8 nucleic acid molecule of claim 97, wherein the nucleic acid molecule is c) or f) and the polypeptide comprises one or more functional domains selected from the group consisting of:

- 20
- a) a transmembrane region;
 - b) a pore loop region; and
 - c) a coiled-coil domain.

109. The TRPM8 nucleic acid molecule of claim 108, wherein the polypeptide comprises a pore loop region flanked by two transmembrane regions.

25 110. The TRPM8 nucleic acid molecule of claim 97, wherein the nucleic acid molecule further comprises a heterologous nucleic acid.

111. The TRPM8 nucleic acid molecule of claim 110, wherein the heterologous nucleic acid comprises a promoter operably linked to the TRPM8 polynucleotide.

5 112. The TRPM8 nucleic acid molecule of claim 110, wherein the heterologous nucleic acid comprises an expression vector.

113. A host cell that comprises a TRPM8 nucleic acid molecule of claim 97.

114. An isolated TRPM8 polypeptide comprising a member selected from the group consisting of:

- 10
- a) a mouse TRPM8 protein comprising amino acid residues 1-1104 of SEQ ID NO: 8;
 - b) a mouse TRPM8 protein comprising amino acid residues 2-1104 of SEQ ID NO: 8;
 - c) one or more functional domains of a mouse TRPM8 protein;
 - d) a human TRPM8 protein comprising amino acid residues 1-1268 of SEQ ID NO 11;
 - 15 e) a human TRPM8 protein comprising amino acid residues 2-1268 of SEQ ID NO 11; and
 - f) one or more functional domains of a human TRPM8 protein.

20 115. The TRPM8 polypeptide of claim 114, wherein the nucleic acid molecule is c) or f) and the functional domains comprise one or more members selected from the group consisting of:

- a) a transmembrane region;
- b) a pore loop region; and
- c) a coiled-coil domain.

25 116. The TRPM8 polypeptide of claim 115, wherein the polypeptide comprises a pore loop region flanked by two transmembrane regions.

117. An antibody that specifically binds to a TRPM8 polypeptide of claim 114.

118. A method for identifying an agent that modulates TRPM8-mediated cation passage through a membrane, the method comprising:

- a) providing a membrane that comprises a TRPM8 polypeptide of claim 114;
- 5 b) contacting the membrane with a candidate agent; and
- c) determining whether passage of one or more cations through the membrane is increased in the presence of the candidate agent compared to passage in the absence of the candidate agent.

119. The method of claim 118, wherein the membrane comprises a cell and
10 cation passage through the membrane is detected by measuring cation influx across the membrane into the cell.

120. The method of claim 119, wherein the cell comprises a promoter operably linked to a heterologous polynucleotide that encodes the TRPM8 polypeptide.

121. The method of claim 118, wherein cation passage through the
15 membrane is detected by voltage clamping.

122. The method of claim 118, wherein cation passage through the membrane is detected by an ion sensitive dye or a membrane potential dye.

123. The method of claim 118, wherein the membrane is contacted with the candidate modulating agent in a well of a multiwell plate.

20 124. The method of claim 123, wherein the multiwell plate is a 96-, 384- or 1536-well plate.

125. The method of claim 118, wherein the assay is to identify antagonists of TRPM8-mediated cation passage and is conducted at a temperature of less than 20°C and/or in the presence of menthol.

25 126. The method of claim 125, wherein a candidate agent that reduces cation passage is further tested for ability to treat pain by administering the candidate agent to a test

animal and determining whether the candidate agent decreases the test animal's response to a pain stimulus.

127. The method of claim 126, wherein the pain stimulus is cold.

128. The method of claim 118, wherein the assay is to identify agonists of
5 TRPM8-mediated cation passage and is conducted at a temperature of greater than 20°C.

129. The method of claim 128, wherein an agonist of TRPM8-mediated cation passage is used as a fragrance or a flavor enhancer.

130. A method of reducing pain associated with TRPM8 activity, the method comprising administering to a subject suffering from pain an analgesically effective amount
10 of a compound that reduces TRPM8-mediated cation passage through a membrane or reduces signal transduction from a TRPM8 polypeptide to a DRG neuron.

131. The method of claim 130, wherein the pain is associated with one or more of cold exposure, inflammation, or tissue damage.

132. The method of claim 130, wherein the compound is selected from the
15 group consisting of:

- a) an antibody that specifically binds to a TRPM8 polypeptide;
- b) an antisense polynucleotide, ribozyme, or an interfering RNA that reduces expression of a TRPM8 polypeptide; and
- c) a chemical compound that reduces cation passage through a
20 membrane that comprises a TRPM8 polypeptide.

133. The method of claim 132, wherein the chemical compound has a molecular weight of 1000 daltons or less.

134. A method for determining whether pain in a subject is mediated by TRPM8, the method comprising:

- 25 a) obtaining a sample from a region of the subject at which the pain is felt; and

- b) testing the sample to determine whether a TRPM8 polypeptide or TRPM8 polynucleotide is present in the sample.

135. The method of claim 134, wherein the presence of a TRPM8 polypeptide in the sample is detected by determining whether cation passage across
5 membranes of cells in the sample is mediated by a TRPM8 polypeptide.

136. The method of claim 135, wherein TRPM8 involvement in mediating cation passage across membranes of the cells is determined by detecting an increase or decrease in cation passage across membranes of the cells when assayed below 20°C and/or in the presence of menthol, compared to cation passage when assayed above 20°C and/or in the
10 absence of menthol.

137. The method of claim 134, wherein the presence of a TRPM8 polypeptide in the sample is detected by contacting the sample with a reagent that specifically binds to a TRPM8 polypeptide.

138. The method of claim 137, wherein the reagent comprises an antibody.

139. The method of claim 134, wherein the presence of a TRPM8 polynucleotide in the sample is detected by contacting nucleic acids from the sample with a test polynucleotide that can hybridize to a TRPM8 polynucleotide.
15

140. The method of claim 139, wherein the test polynucleotide comprises an oligonucleotide at least 10 nucleotides in length.

141. The method of claim 139, wherein the method comprises amplification of a TRPM8 polynucleotide, if present in the sample.
20

142. The method of claim 141, wherein the amplification comprises polymerase chain reaction or ligase chain reaction.

143. The method of claim 139, wherein the test polynucleotide is attached to
25 a solid support.

144. The method of claim 143, wherein the solid support comprises a microchip.

145. A method for identifying an agent useful in the modulation of a mammalian sensory response, the method comprising:

- 5 a) contacting a candidate agent with a test system that comprises a receptor polypeptide selected from the group consisting of TRPM8, TRPV3 and TRPV4; and
- b) detecting a change in activity of the receptor polypeptide in the presence of the candidate agent as compared to the activity of the receptor polypeptide in the absence of the agent, thereby identifying
- 10 an agent that modulates receptor activity.

146. The method of claim 145, wherein the sensory response is response to cold and the polypeptide is a TRPM8 polypeptide.

147. The method of claim 146, wherein the TRPM8 polypeptide comprises an amino acid sequence as set forth in SEQ ID NO: 8 or SEQ ID NO: 11.

15

148. The method of claim 145, wherein the sensory response is response to warm or hot temperatures and the polypeptide is a TRPV3 polypeptide.

149. The method of claim 148, wherein the TRPV3 polypeptide comprises an amino acid sequence as set forth in SEQ ID NO: 2 or SEQ ID NO: 5.

20 150. The method of claim 145, wherein the sensory response neuropathic pain and the polypeptide is a TRPV4 polypeptide.

151. The method of claim 150, wherein the TRPV4 polypeptide comprises an amino acid sequence as set forth in SEQ ID NO: 14 or SEQ ID NO: 17.

25 152. The method of claim 145, wherein the method further comprises administering the agent that modulates receptor activity to a test subject, and thereafter detecting a change in the sensory response in the test subject.

153. The method of claim 145, wherein the test system comprises a membrane that comprises the receptor polypeptide.

154. The method of claim 153, wherein the test system comprises a cell that expresses a heterologous polynucleotide that encodes the receptor polypeptide.

5 155. The method of claim 154, wherein the cell is substantially isolated and the contacting is performed *in vitro*.

156. The method of claim 154, wherein the cell is present in an organism and the contacting is performed *in vivo*.

10 157. The method of claim 145, wherein the receptor activity comprises increased or decreased Ca^{2+} passage through the membrane that comprises the receptor polypeptide.

158. The method of claim 157, wherein the membrane comprises a substantially purified cell membrane.

159. The method of claim 157, wherein the membrane comprises a liposome.

15 160. A method for monitoring the efficacy of a treatment of a subject suffering from pain, the method comprising:

- a) obtaining, at two or more time points in the course of treatment for pain, a sample from a region of the subject at which the pain is felt; and
- 20 b) testing the samples to determine whether a reduction is observed from one time point to another in amount or activity of one or more members selected from the group consisting of: a TRPV3 polypeptide, a TRPV3 mRNA, a TRPV4 polypeptide, a TRPV4 mRNA, a TRPM8 polypeptide, and a TRPM8 mRNA.

25 161. The method of claim 160, wherein one of the time points is prior to administration of the treatment for pain.

162. An assay capable of detecting the expression of one or more of TRPV3, TRPV4 or TRPM8 in human tissue, the assay selected from the group consisting of:

- a) an assay comprising contacting a human tissue sample with monoclonal antibodies binding to TRPV3, TRPV4 or TRPM8 and determining whether the monoclonal antibodies bind to polypeptides in the sample; and
- b) an assay comprising contacting a human tissue sample with an oligonucleotide that is capable of hybridizing to a nucleic acid that encodes TRPV3, TRPV4 or TRPM8.

163. The assay of claim 162, wherein the assay comprises contacting a human tissue sample with a pair of oligonucleotides that are capable of hybridizing to a nucleic acid that encodes TRPV3, TRPV4 or TRPM8 and subjecting the sample to polymerase chain reaction.

164. The assay of claim 162, wherein the assay comprises contacting a human tissue sample with an oligonucleotide array that comprises one or more oligonucleotides that are capable of hybridizing to a nucleic acid that encodes TRPV3, TRPV4 or TRPM8.

165. The assay of claim 162, wherein the human tissue sample is obtained from a site of pain.

166. A method of treating pain, the method comprising identifying a patient suffering from pain mediated by one or more polypeptides selected from the group consisting of TRPV3, TRPV4 and TRPM8 by measuring expression of the polypeptide in tissue from such patient, and administering to such patient an analgesically effective amount of an agent which inhibits the polypeptide.

167. A method for identifying an agent useful in the treatment of pain, the method comprising:

- a) administering a candidate agent to a mammal suffering from pain;
- b) in a sample obtained from the mammal, detecting an activity or amount of one or more members selected from the group consisting

of: a TRPV3 polypeptide, a TRPV3 mRNA, a TRPV4 polypeptide, a TRPV4 mRNA, a TRPM8 polypeptide, and a TRPM8 mRNA; and

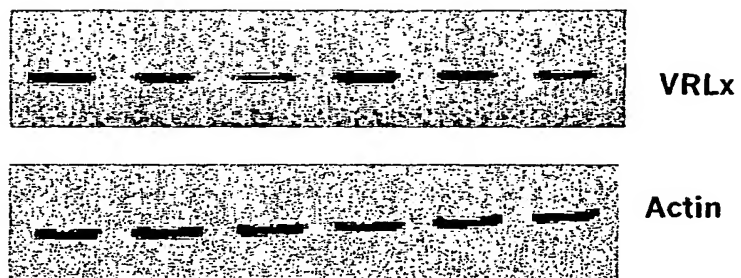
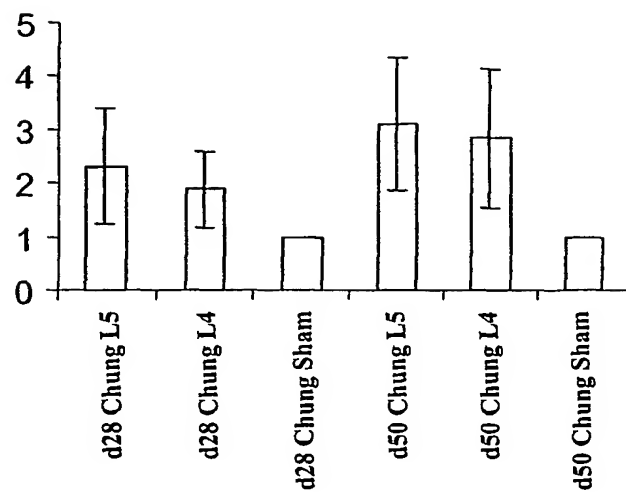
- c) comparing the amount or activity of the member in the presence of the candidate agent with the amount or activity of the member in a sample obtained from the mammal in the absence of the candidate agent, wherein a decrease in amount or activity of the member in the sample in the presence of the candidate agent relative to the amount or activity in the absence of the candidate agent is indicative of an agent useful in the treatment of pain.

10 **168.** A method of identifying an agent that binds to and/or modulates the activity of an mRNA or polypeptide encoded by a TRPV3, TRPV4, or TRPM8 nucleic acid, the method comprising:

- 15 a) contacting an isolated cell which expresses a heterologous TRPV3, TRPV4, or TRPM8 nucleic acid encoding a polypeptide with the agent; and
- b) determining binding and/or modulation of the activity of the mRNA or polypeptide by the agent, to identify agents which bind with and/or modulate the activity of the polypeptide.

A

RT-PCR

Fold
Regulation

B

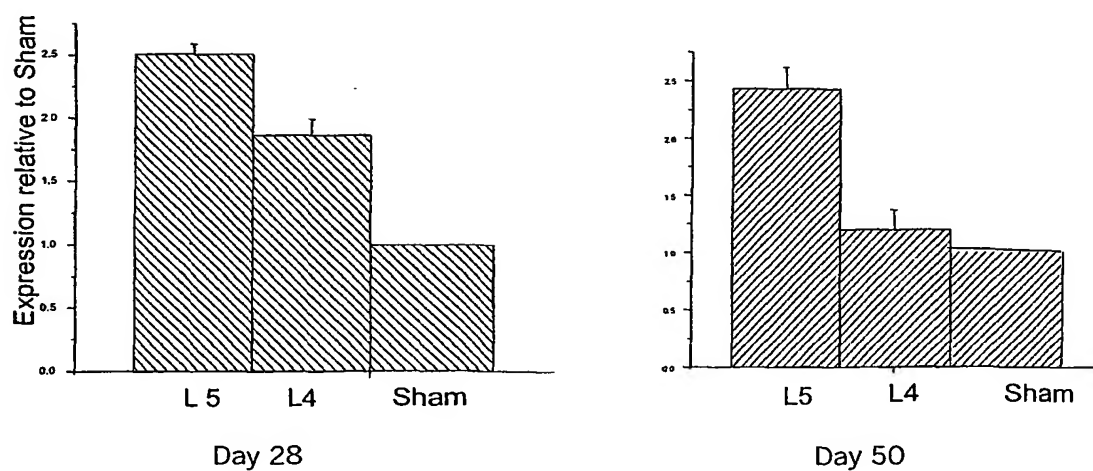


Figure 1

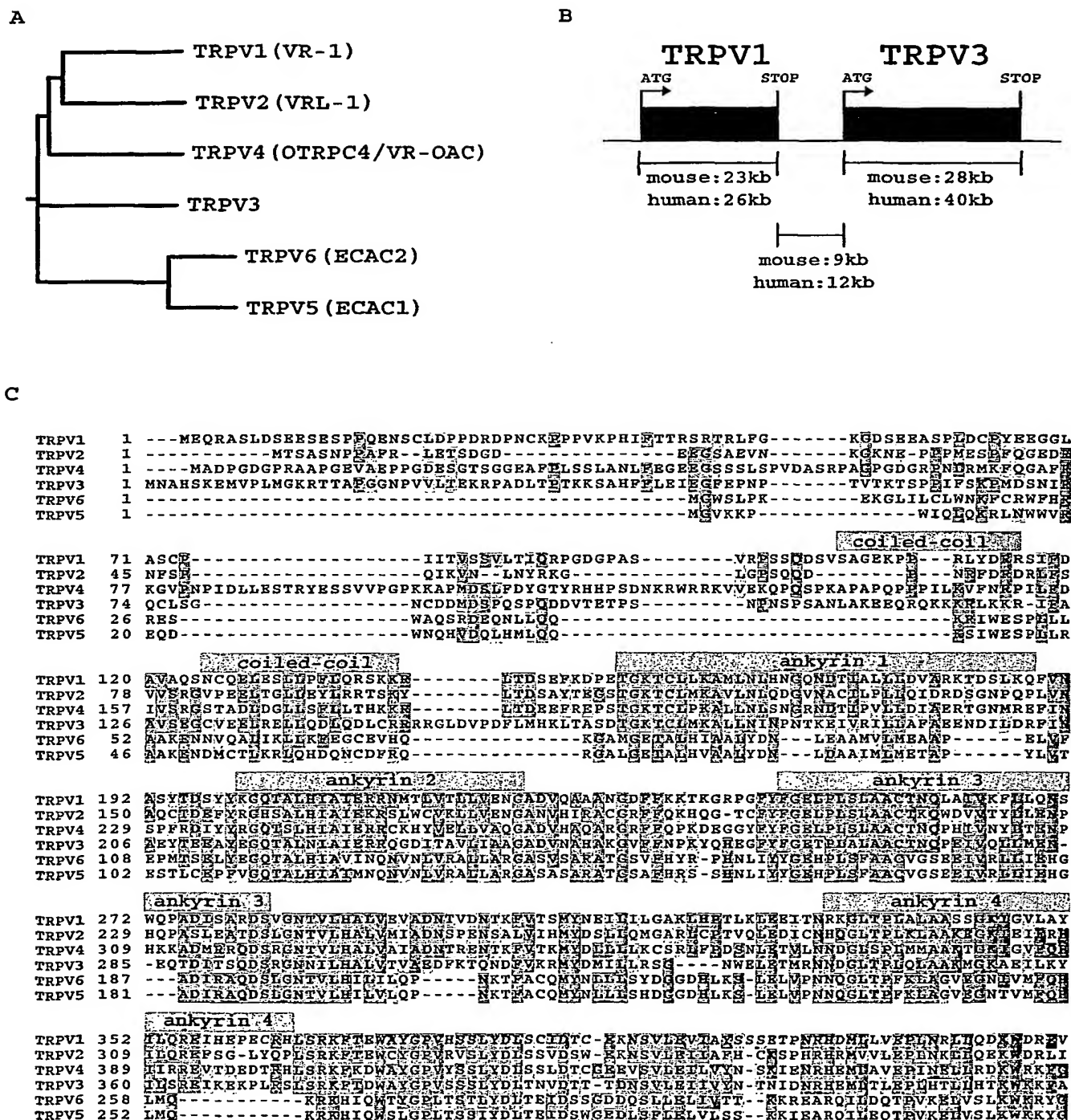


Figure 2

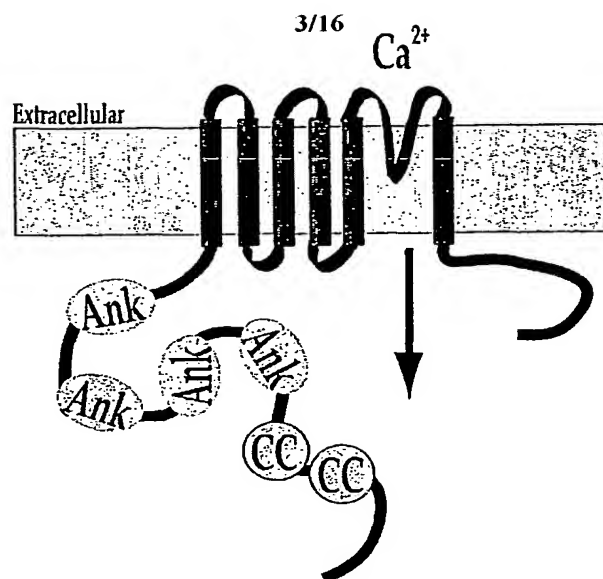
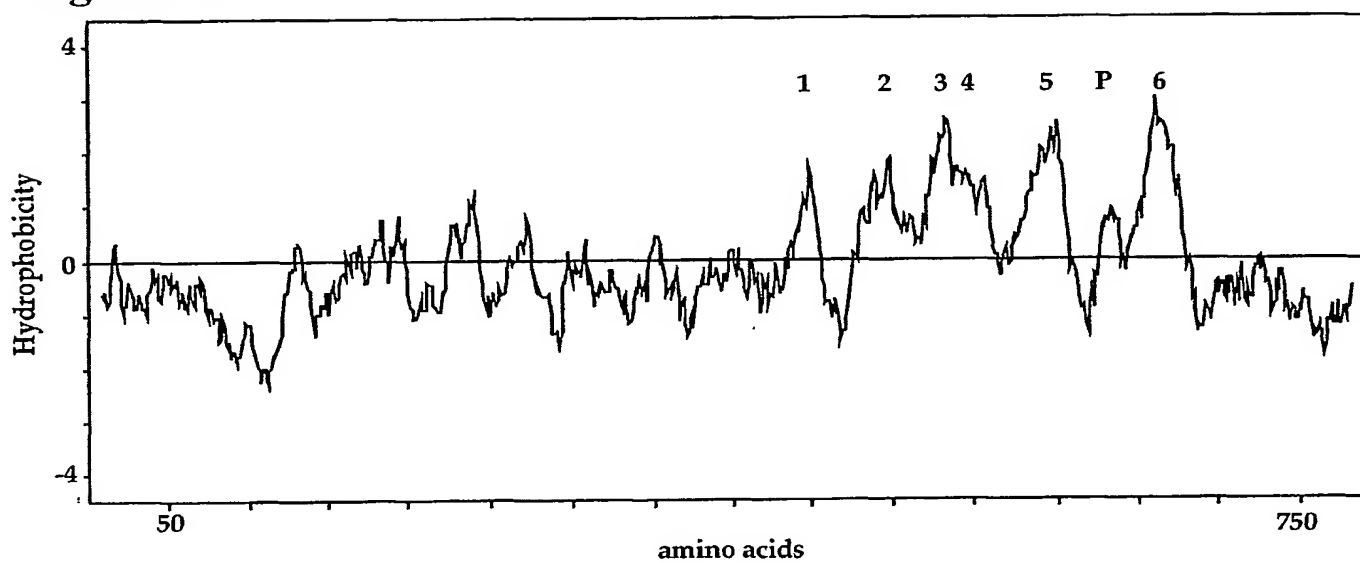
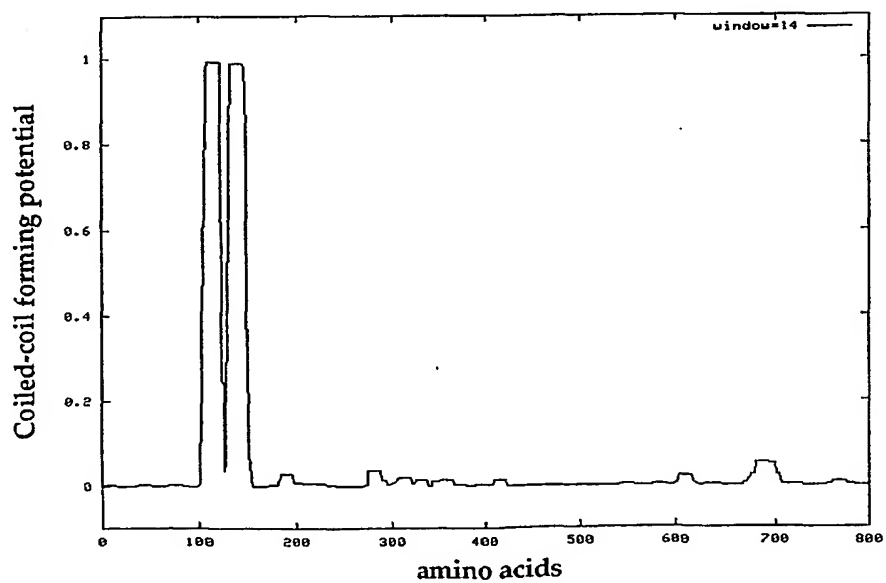
Figure 2D**Figure 2E****Figure 2F**

Figure 3

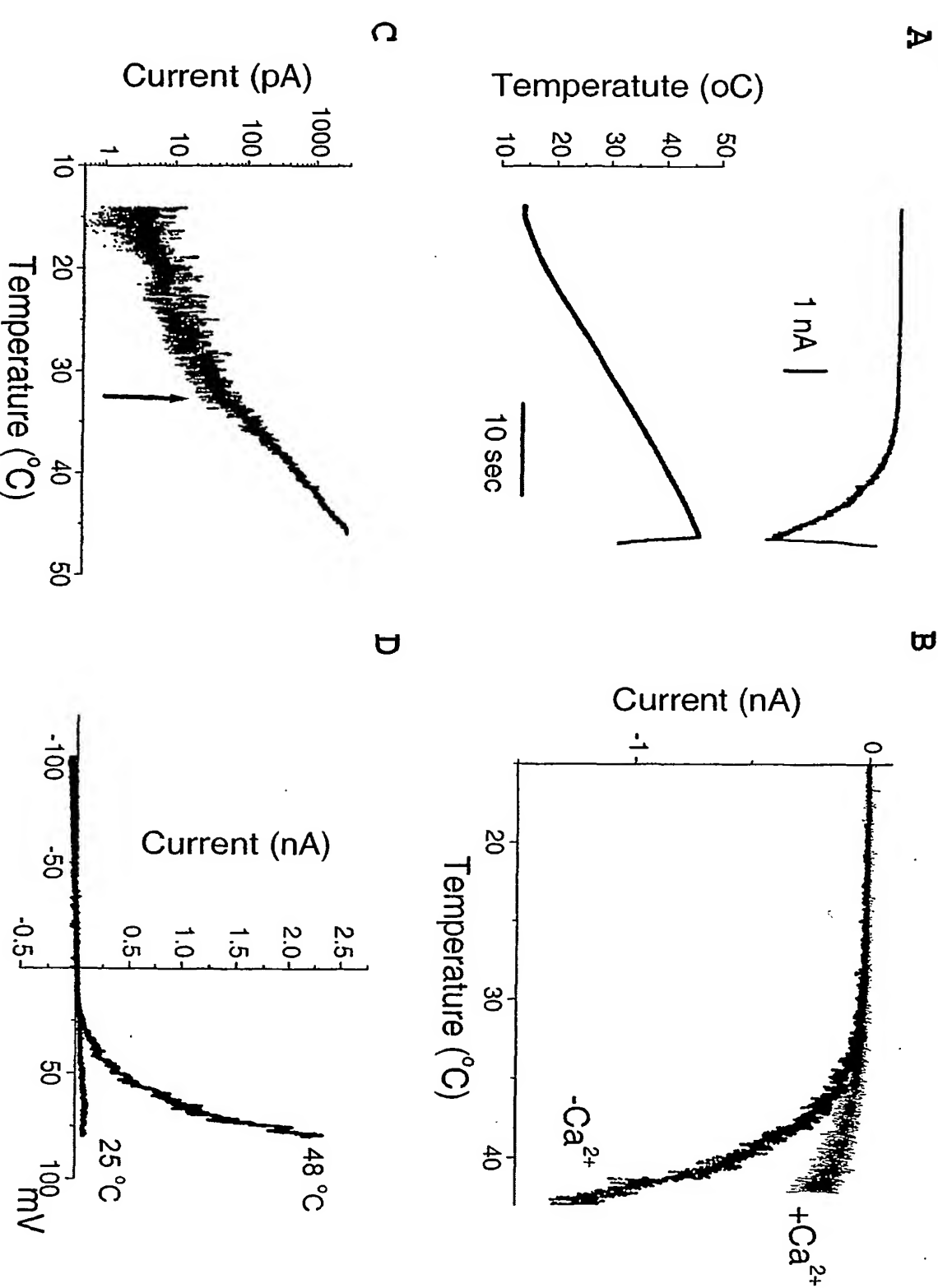
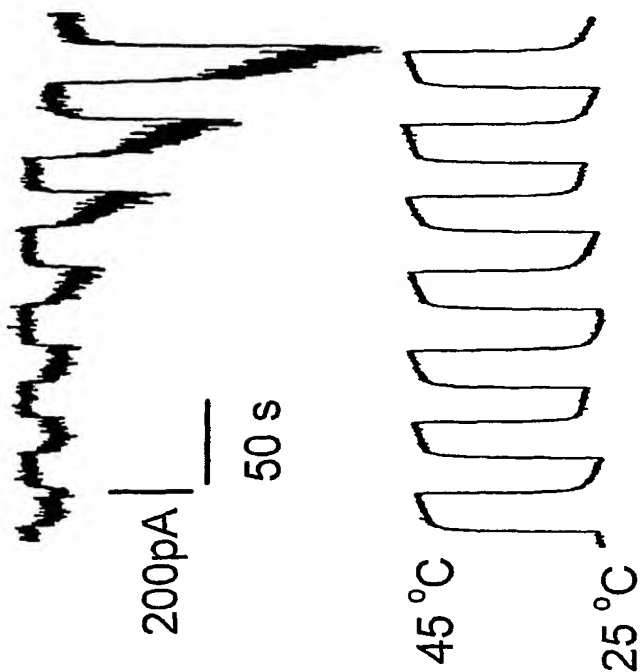
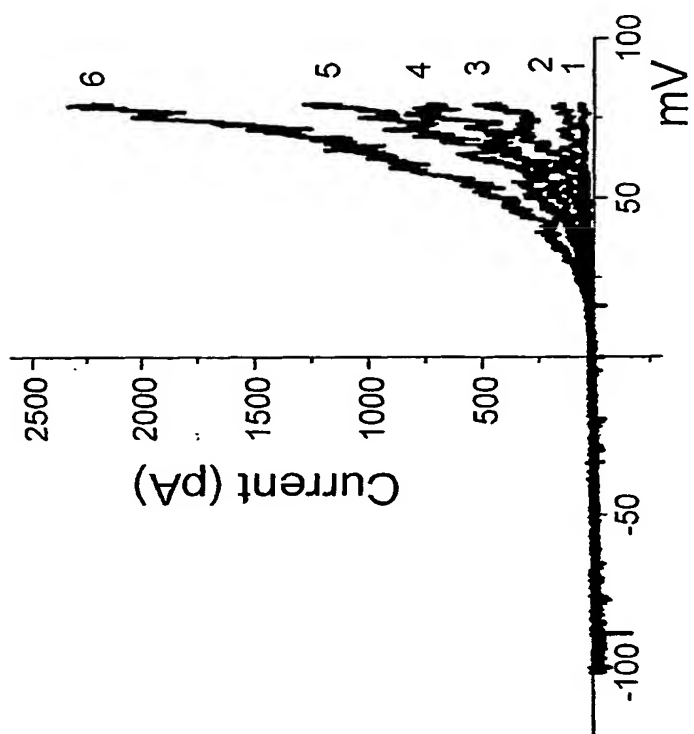


Figure 7

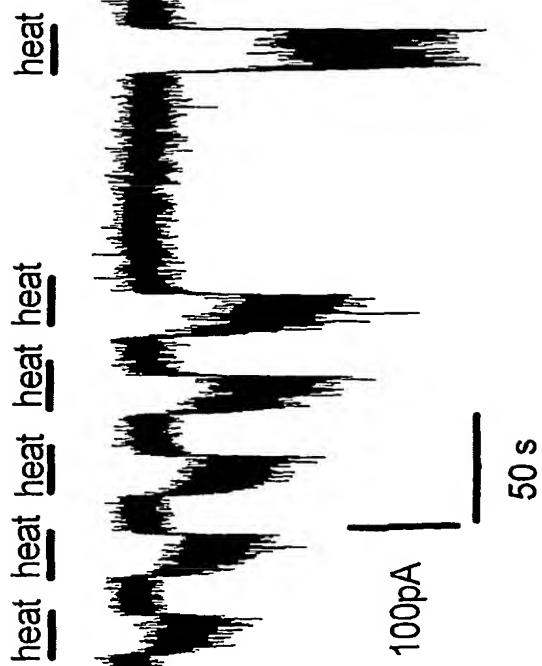
A



B



C



D

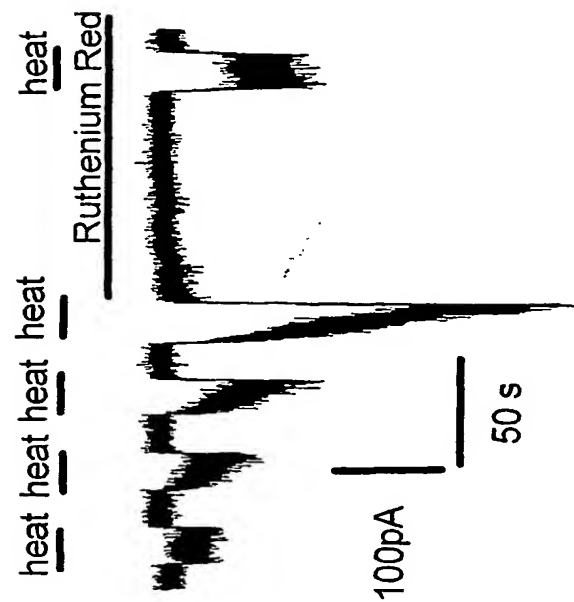


Figure 5

6/16

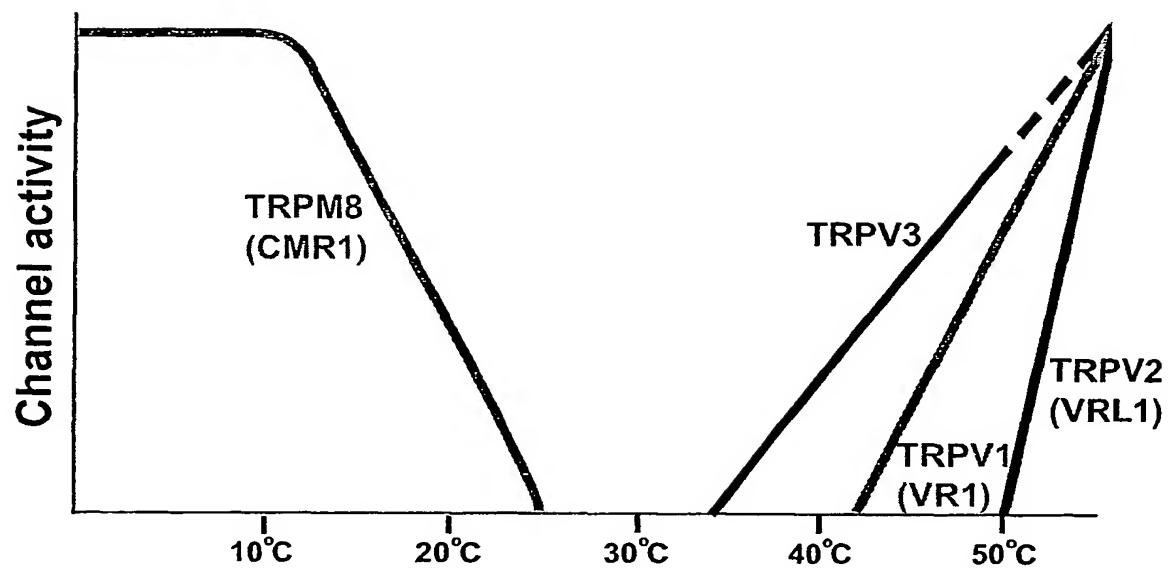


Figure 6A

TRPM7 1 MSQKSWIESTLTKRECVY-----IIPSSKDPHRCPLPGCQYICQQTVCFCGRLLVKQHA
TRPM1 1
TRPM2 1 MEPSALRKAGSEQEGFELPRRVTDLCMVSNRRSSNSLFFKSWRLQCFFGNNDKQESIPSSWIPENIKKKKCVYFVSSSK
TRPM8 1 MSFEGARLSMRERRNGTMCSTR-----TLVSSVSRST-----DVSYSDSD-----LVNFIQANPKKRECVFFTRDSK

TRPM7 53 CFTASLAKMYSVDKLGEBHFNQA-----IPSSVSEKHTBQSPTDAYGVINEQGGSHSYRAKYVRLSYDTRPEITLQALL
TRPM1 1
TRPM2 81 LSDAGKVVCOGCTHEQHLBEATKPTFGQTQDPKKHVQEMPTDAFGDIVFTGLSQV-KKYVRVSQDTPSSVLYHLMV
TRPM8 63 AMEN---ICKCGYAAQSQHIEGT---QINQNEKNYKKHTKEFPPTDAFGDIQETLGGKG-K-YLRLSCDTSSTLYELLT

TRPM7 126 KENQMLEPLKLVISVHCGMQRFELHPRIKQLGKGLIKAAVTTGANILTGGVNTGVAKHVGDALKEHARRSSRK---ICTI
TRPM1 20 KDMOLELPKLLISVHGGLONFEMQPKLKQVFGKGLIKAAMTTGAWIFTGGVSTGVISHVGDALKDHSSKSGR---VCAI
TRPM2 160 QHWGLDVPNLLISVTGGAKNFNMKPLKLSIFRRGLVKVAQTTGAWITGGSHTGVMKQVGEAVRDPSSLSSSYKGBELITI
TRPM8 135 QHWHLKTENLVISVTGGAKNFALKPRMRKIFSR-LIIVIAQSKGAWILTTGGTHVGLMKYIGEVVRDNTISRNSEE-NIVAI

TRPM7 203 GIAPWGVNIENRDLVG-----RDVVPYQTLNPLSKLNVNLSHSHFILVDDGTGKYGAEVRLRRELEKRTINOOR-TH
TRPM1 97 GIAPWGVNIENKEDLVG-----KDVHVVYQTMSPNLSKLVNLSHSHFILADNGTLGKYGAEVRLRRELEKRTINOOR-TH
TRPM2 240 GVATNGTVHRRREGLIHTP---GSFPAYILDEDDGGNLTCLDSNHSHPILVDDGTGQVGVETPLRTRLEKPTISEQTKER
TRPM8 213 GIAANGVSNRDLTIRSCDDEGHFAQYIMDPTDRDPTVLDNNHSHHLLVDDNGCHGHTVEAKLRNQLERYISERTSQD

TRPM7 277 ARICQGVVVALTEEGGNVILTEVLEQSEPPVPVVCETGTRAADLLAYIHKQTEEGGNLPDAAEPDITISTIKKTFNF
TRPM1 171 TRLGQGVPLGLVVEGGPNVSVIVLEYLOEPPPIPVICDGSGRASDILSFARKYCEGGIINESLREQLLVTIQKTFNY
TRPM2 317 GGVAKKIPVVCVLEGGPGTLLTIDNATTN--GTPCVVVEGSGRVADVIAQVANLPVSDITISLQOKLSVEFQEMFETP
TRPM8 293 SNYGRIPVPCFAQGGRETLLKATNVS-KIPCVVVEGSGQIADVIASLEV-EDVLTSSMVKERLVRLVTRSL

TRPM7 357 GQSSAVHLFQTMMECMKKKELITVFHIGSEBHDODIVAILTALLKGTNASAPD-----QLHLLAWDRVDIAKNHVFV
TRPM1 251 NKAQSHQLFAITMECMKKKELITVFHIGSEBHDODIVAILTALLKGTNASAPD-----QLHLLAWDRVDIAKNHVFV
TRPM2 395 TESRFVWTKKLODIVRRQOLLTVREKQDQODVAILQALLKASRSQDHFHGHENWHDOLKLAVALNRVDIARSEIFM
TRPM8 370 PEEBIESWIKWREILBSSHLLTVIKMERAGDEIVSNALISYALYKAFSTNEQD-KDNWNGQLKLLLEWNOOLDASDEIFT

TRPM7 430 YGQQLL
TRPM1 324 EGPHETPLGSLAPPTDSKATEKEKKPPMATTKGGRGKGGKGGKGVKKEVEEETDPRRIELLNWVNALEQAMLDALVDR
TRPM2 475 DEWQNP
TRPM8 449 NDRRWES-----ADLQVMTALIKDR

TRPM7 452 VSFVKLLIENGVSMMKFLTIPRLEELYNKQGPPTNPMDFHLIRDVKQGN---LPPGYKITLIDIGLVIEYLMGGTYRGT
TRPM1 404 VDFVKLLIENGVSMMKFLTIPRLEELYNKQGPPTNPMDFHLIRDVKQGN---LPPGYKITLIDIGLVIEYLMGGTYRGT
TRPM2 497 PEFVKLFLENGVOLKEPVTDWTLVLYLENLDFSCLFHSLKQKVLVEDPERPACAPAPFLOMHHVAQVRLLELGDDETQFL
TRPM8 471 PKFVRFLFLENGVOLKEPVTDWTLVLYLENLDFSCLFHSLKQKVLVEDPERPACAPAPFLOMHHVAQVRLLELGDDETQFL

TRPM7 528 YTRKRFRLLYNSGCGNRRSGRNTSSSTPQRRKSHETFGNRADPKBEKMRHNFIKTAQPYRPMKDMASMEEGKKKRTKDEI
TRPM1 479 YTRKRFRLLYNSGCGNRRSGRNTSSSTPQRRKSHETFGNRADPKBEKMRHNFIKTAQPYRPMKDMASMEEGKKKRTKDEI
TRPM2 577 YPRPRHNDRLRLLLP-----YHVKLVNQCVSLRSYKRSSTG-----KKRKKKESID
TRPM8 536 WKEDRSSR-----EDLDVELHDASLT

TRPM7 608 VDIDDPETKRFYPLNELLIAWCLMKRQVMARFLWQGEESMAKALVACKIYRSMAYEAKQSDLVDDTSEELKQVSNDFG
TRPM1 528 IDVDDPAVSFPQYFPHLMVWVLMKROKMAVFLWQGEESMAKALVACKIYRSMAYEAKQSDLVDDTSEELKQVSNDFG
TRPM2 615 -----VFTMDPFDRIWIAVQNRRLAGIIVWQSDCIAALACSILKELKEED-----TDSSSEDLNABEVE
TRPM8 557 -----TRHPLQALFIWAILQNKRELSKVIVWQCTKGCTLAALGASKLKTLAKVKND-----INAGSESEELANEVE

TRPM7 688 QLAVELLEQSFRODETAMKLLTYELKNWSNSTCLKLAUSSRLRFVFAHTCTOMLSDMMWGRNLMNRKNSWYKVLISILV
TRPM1 608 QLAVELLDQSKHDEQAMKLLTYELKNWSNSTCLKLAUSSRLRFVFAHTCTOMLSDMMWGRNLMNRKNSWYKVLISILV
TRPM2 684 HRAIGVFTECYRKDEBRAQKLLTRVSEAWGKTTCLQALEAKDMKFVSHGGIQAFLTKVWVGQLSVDNGLWRYTLCLDAF
TRPM8 623 TRAVELFTCYSDNDEDLAEQLLVYSCEAWGGSNCCLAVAEATDQHFIAQPGVQNPFLSKQWVGEISRDRTNWKIILCFII

TRPM7 768 PPAILLMLEYKTKAEMSHIPQSQDAHQMTMEDSENFNHITKIPMEVFKSVKILSSDGKNEMBIHIKSKRLPITRKCYA
TRPM1 688 PPAILLMLEYKTKAEMSHIPQSQDAHQMTMEDSENFNHITKIPMEVFKSVKILSSDGKNEMBIHIKSKRLPITRKCYA
TRPM2 764 PLLLTGLISPREKRLQDVG-----EN-----TDANADAGSRKGDENEHKKORSIPGKTICE
TRPM8 703 PLVGCGLVSPREKPIDKHK-----KLLWYVVA

TRPM7 848 FYHAPIVKWFENTLALYGLMLYTFVVLVKMEQLPSVOEWIVYAYIFTALIEKVREVFMS-EAGKISQIKVWFSDFNV
TRPM1 753 FYHAPIVKWFENTLALYGLMLYTFVVLVKMEQLPSVOEWIVYAYIFTALIEKVREVFMS-EAGKISQIKVWFSDFNV
TRPM2 791 FETAPVVVPHLNLISYFAFLCLFAYVLMVDFQPVPSWCECAIYVWLFSLVCEEMRQLFYDPEECGLMKKALAYFSDFWNK
TRPM8 730 FETSPFVVVPSWNLVSYFAFLCLFAYVLMVDFQPVPSWCECAIYVWLFSLVCEEMRQLFYDPEECGLMKKALAYFSDFWNK

TRPM7 927 SDTIAISIFVGFGLRFGAKWNYINAYDNHVFVAGRLIYCLNLIIFWYVRLLDPLAVNOQAQGYVMMIGKMANMFFVIVV
TRPM1 832 TDVLAISTFMIGAILRLQNP-----YMGYGRVIVCVDIIFWYVRLLDPLAVNOQAQGYVMMIGKMANMFFVIVV
TRPM2 871 LDVGAILLFVAGLTCLIP-----ATLYPGRVILSLDFILFCLRLMHIFTISKTLGKRIIVVGRMMMDVFFFLFL
TRPM8 801 MDITGLFYPIAGIVFRLRSSNK-----SSLYSCRVIFCLDYLIETLRLIHFIVVSRNLGPKIIMLQRLIDVFFFLFL

TRPM7 1007 MALVLLSFGVPRRAILPHERPSSWLSAKDIVFHPYMMIFGEVY-----AYRIDVCANDSTLPT-----ICG
TRPM1 903 MDVVLMSFGVARQAILHPBEKPSWKLARNIYFMYPMIYGEVY-----ADQIDLYAMENPPCGENLYDEEGKRLPFCI
TRPM2 941 LAVVVLVSFGVARQAILHNERRDVLPFGAVYHSYLTIFGQIPGYIDGVNFENPHCSPPNGTDPYKPKCPESDATQCPAF
TRPM8 874 FAVVWVAFSGVARQAILRQNEQRWRWIFRSVIYRPYLA MFQVPSDVSSTTYDFSECTFSGNE-SKPLQVELDEHN-LPRF

TRPM7 1068 PGTWLTFFPQAVYLEVQYIIMVNLIIAFENNVLQVKAISNVWVKYQRYEFIMAYHEKPVLPPLIILSHIVSTFCVVCV
TRPM1 977 PCAWLTAPMAAYLLVANILLVNLIIAFENNVLQVKAISNVWVKYQRYEFIMAYHEKPVLPPLIILSHIVSTFCVVCV
TRPM2 1021 PSEWLTVLCLCLYLFETNILLNLLIAMFNYTEQVQVQEHDTQIKWFPQEDLIBEYHGRPAAPPFFILLSHLOLEKRAVVL
TRPM8 952 PSEWITIPVCIYMSSTNILLVNLIIAFENNVLQVKAISNVWVKYQRYEFIMAYHEKPVLPPLIILSHIVSTFCVVCV

TRPM7 1148 RKKKDKTS-----GPKLFTEEDOKKLFDFEEQCVEMYPDEKDDKFNSSGSEERIRVTFERVEQMSIOLKEVG-DRVNY
TRPM1 1057 RCKKKRSGDQBERDRGKLLFLSDEBRLHEPEQCVQHRFEKEDQOSSSDERIRVTSERVENMSRLEEIM-ERETP
TRPM2 1100 KTPAKRH-----KQKNNKDEKNEBAALLSWETLYKENYLNQRFQKQRPQKIEDISNKKVDAMVDLDDLPKRSKS
TRPM8 1031 CCKKEKN-----MESNACFRNEENETLAWGACVMKENYLVKINTKANDNSEE

TRPM7 1221 IKRSLQSLDSQIGHMODLSALTVDLTMTAQAQASEASKVNEITRSLISKHLAONLIDDVVPVRPLWKKPSAVNTLSSS
TRPM1 1136 MKTSLQTVDLRLAOLBELSNRMVNALENLAGIDRSDLIQAASRASSCEBATYLRQSSNSADGYSLYR-----
TRPM2 1173 MEQRLASLEQVQAOTARALHNVRLTASGFSSEADVPTASQKAAEPDABPGGRKKTEPPGDS-----
TRPM8 1078 MRHRFRQIDSEKLNDEKSELKEHANNK-----

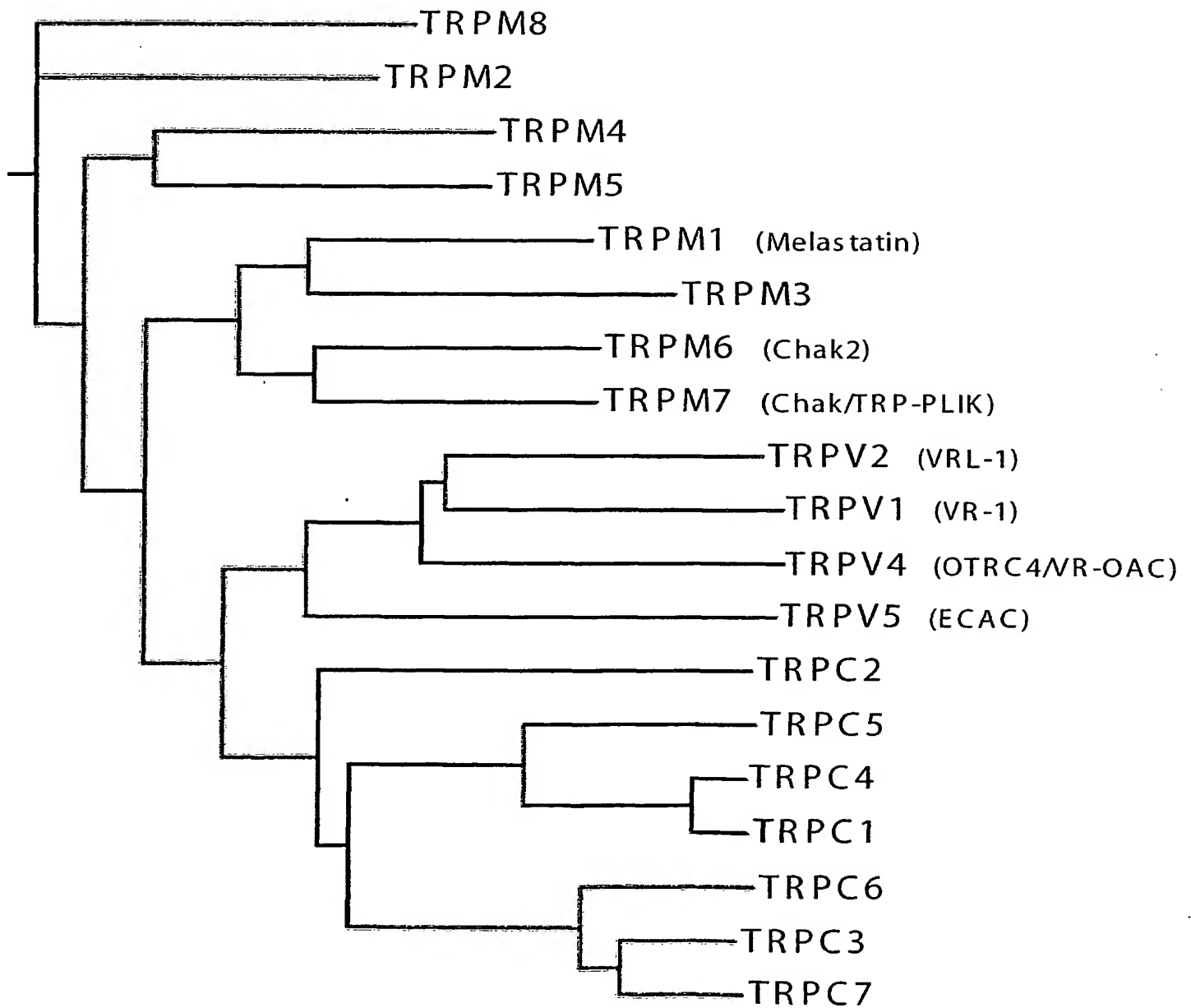
Figure 6B

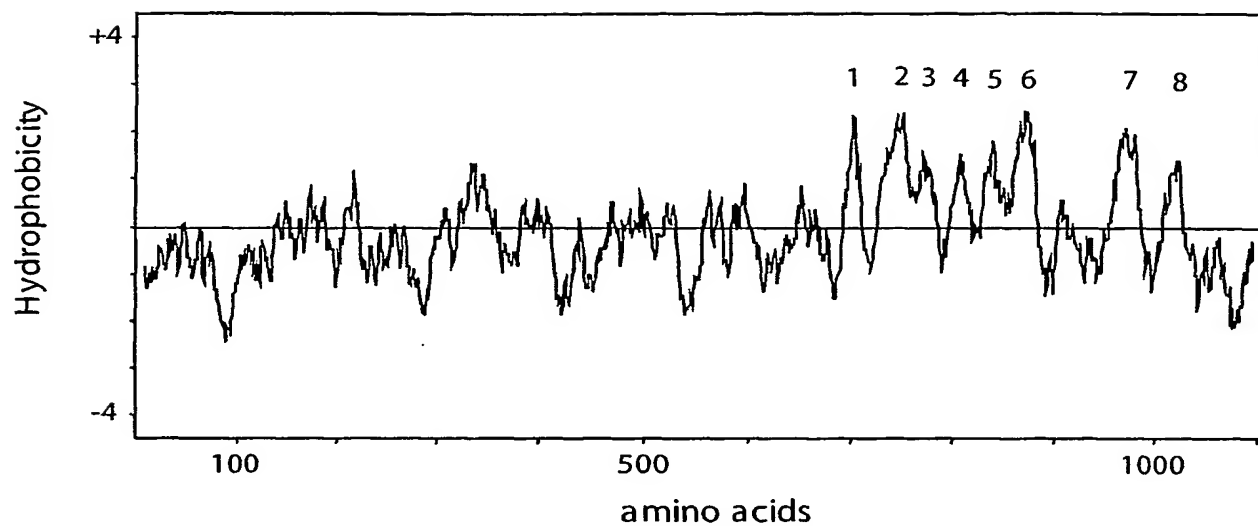
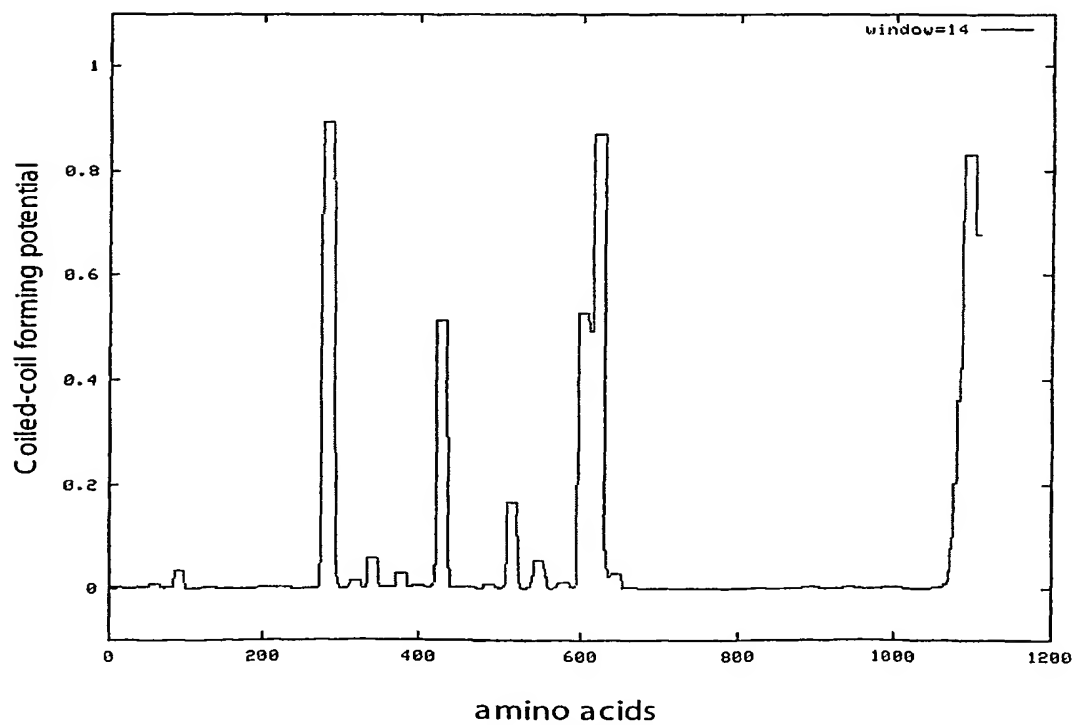
Figure 6C**Figure 6D**

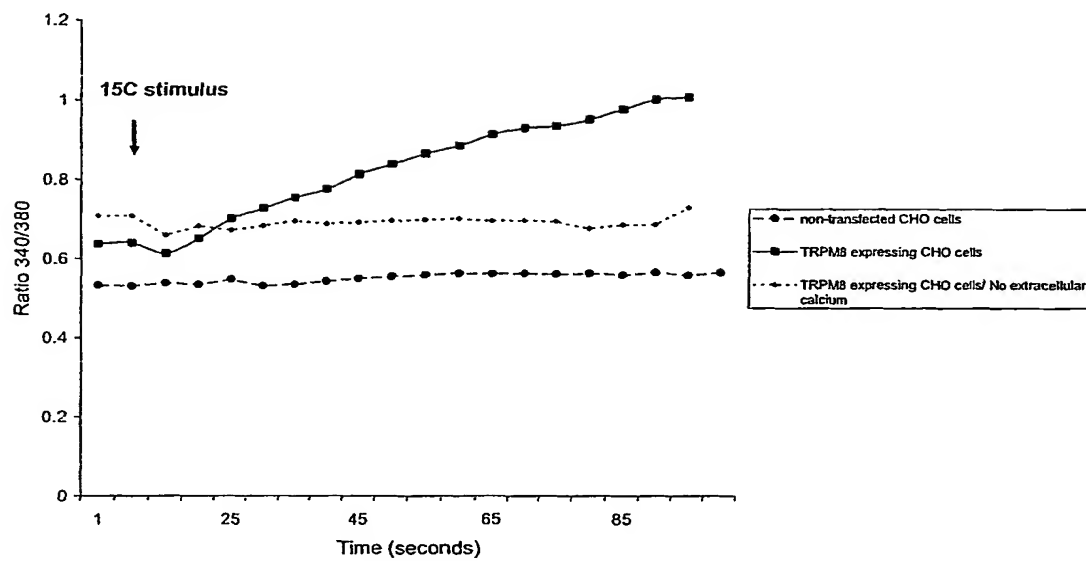
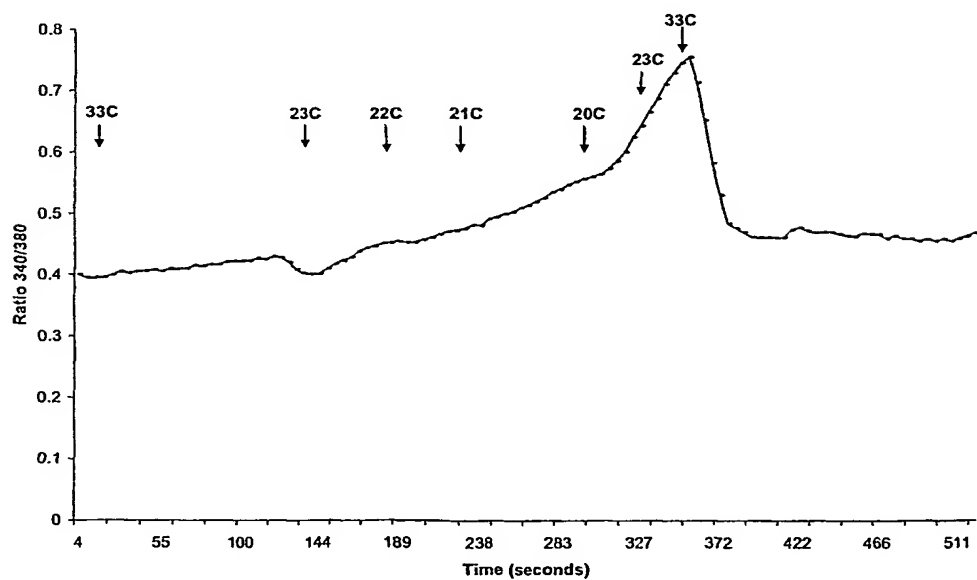
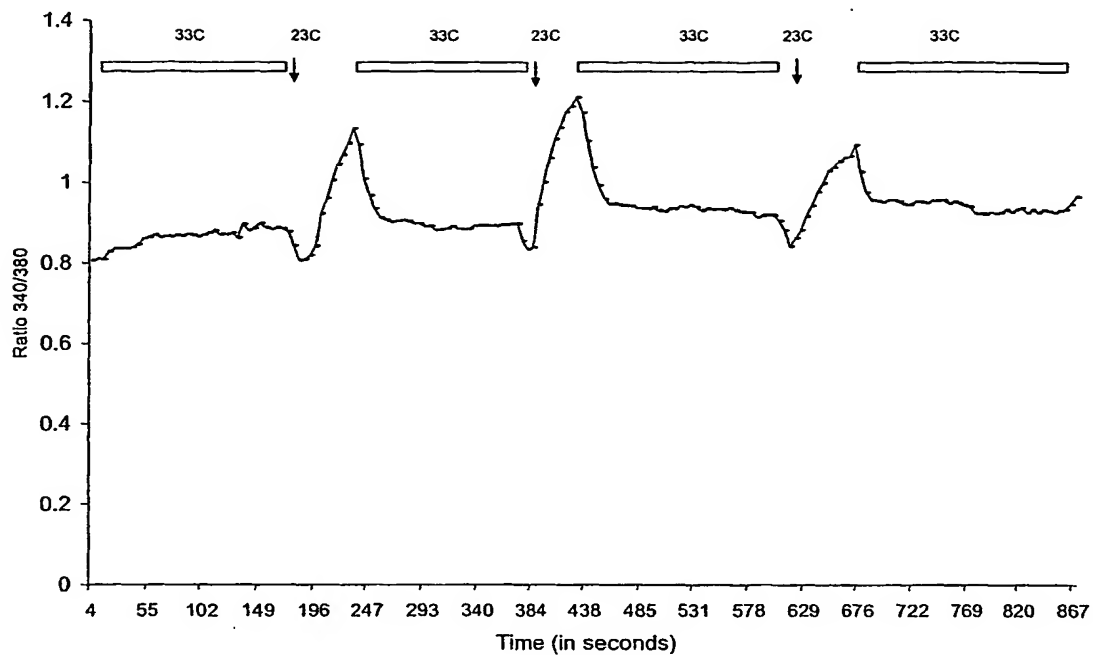
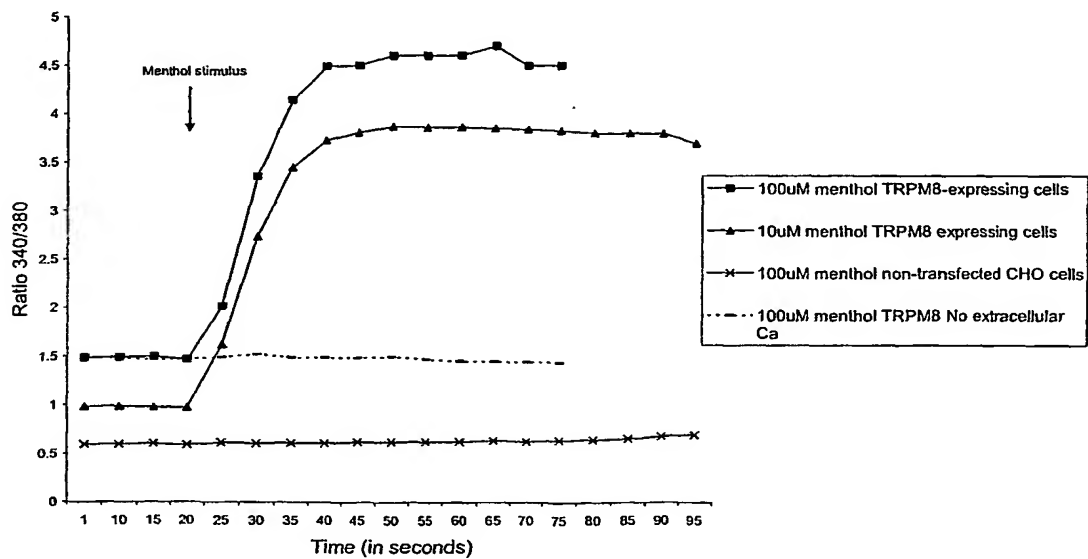
Figure 7A**Figure 7B**

Figure 7C**Figure 7D**

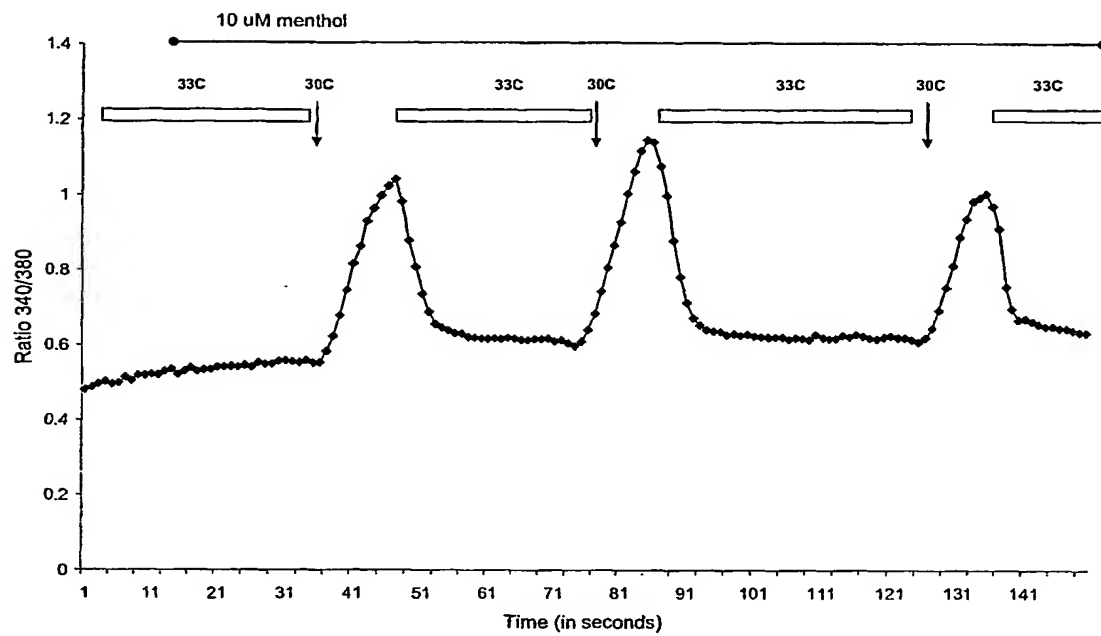


Figure 8

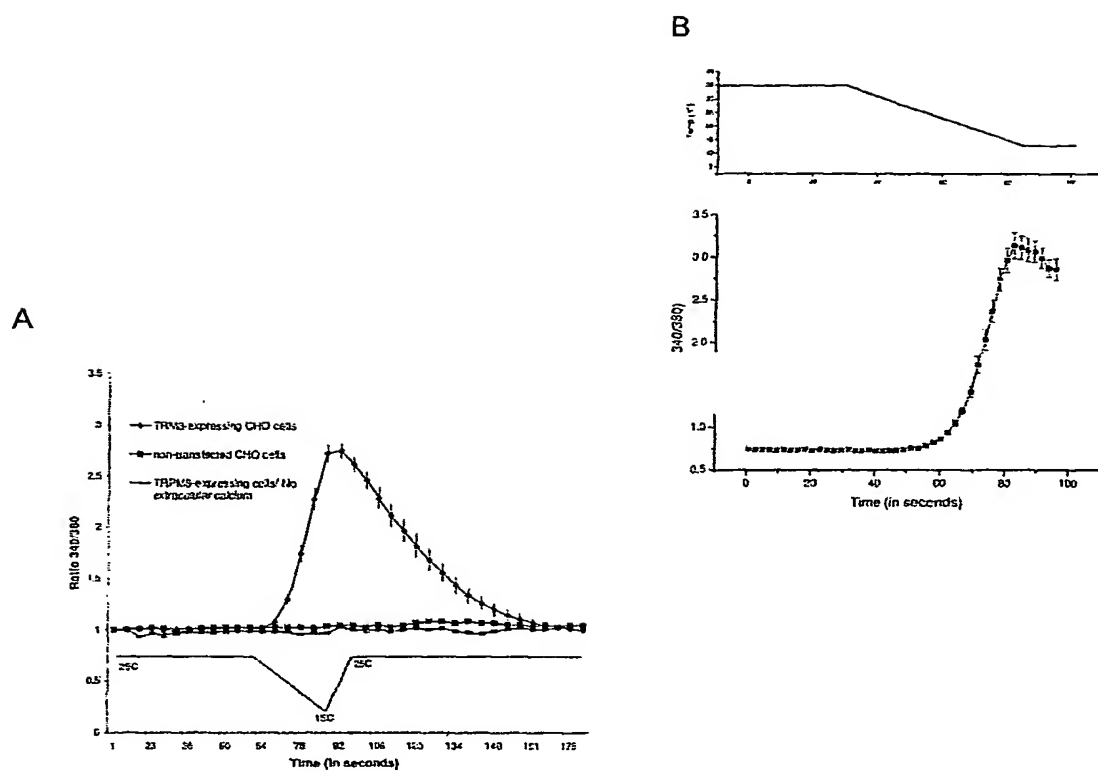


Figure 9

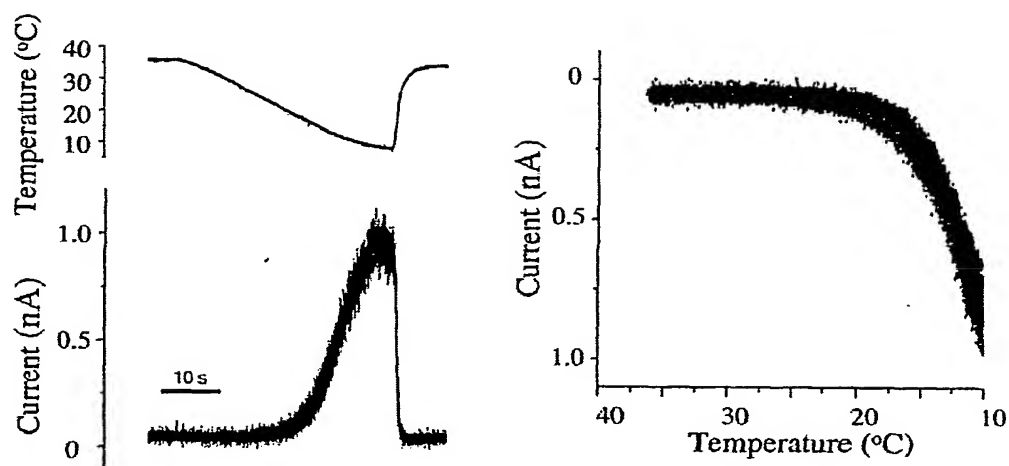
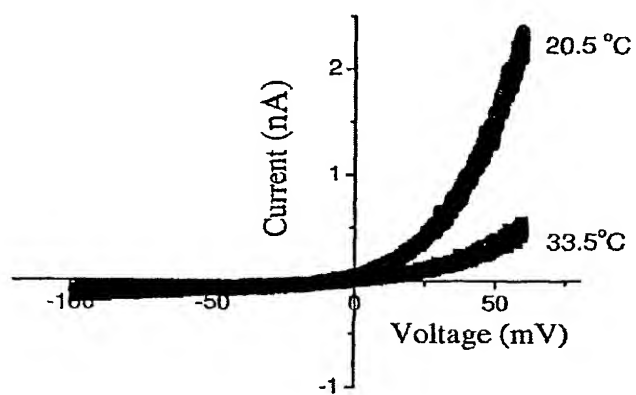
A**B**

Figure 10

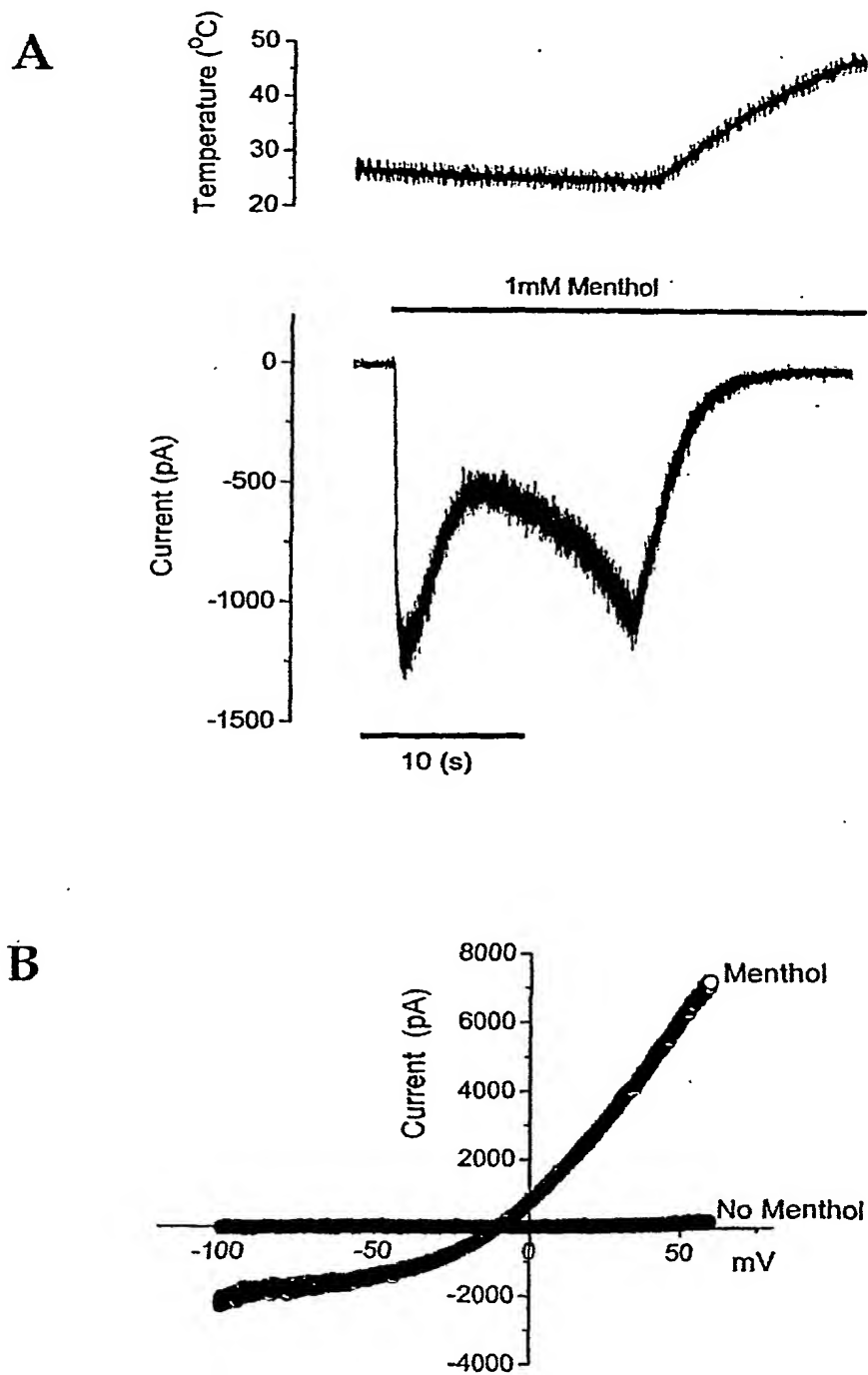
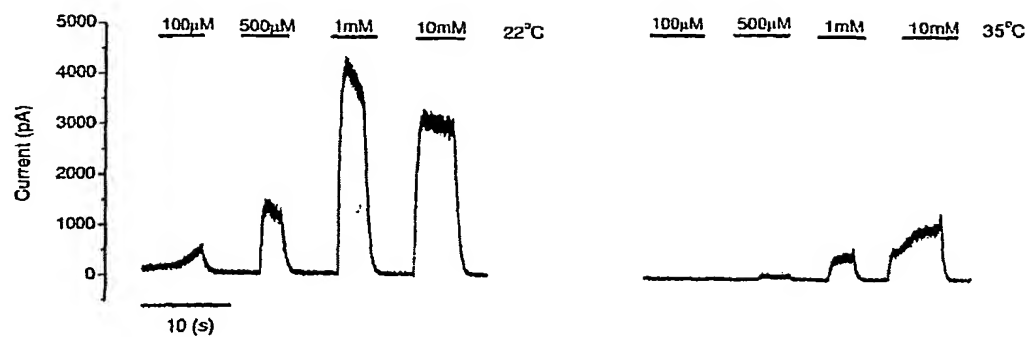
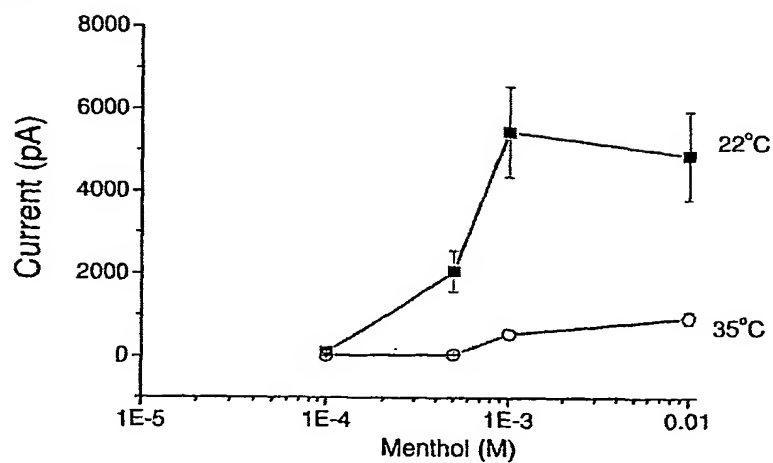


Figure 11

A**B**

SEQUENCE LISTING

<110> Ardem Patapoutian
 Andrea Peier
 Peter McIntyre
 Stuart Bevan
 Chuangzheng Song
 Pamposh Ganju

<120> VANILLOID RECEPTOR-RELATED NUCLEIC ACIDS
 AND POLYPEPTIDES

<130> P0018US60

<150> 60/297,835

<151> 2001-06-13

<150> 60/351,238

<151> 2002-01-22

<150> 60/352,914

<151> 2002-01-29

<150> 60/357,161

<151> 2002-02-12

<150> 60/381,086

<151> 2002-05-15

<150> 60/381,739

<151> 2002-05-16

<160> 114

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 2440

<212> DNA

<213> Mus musculus

<220>

<221> CDS

<222> (65)...(2440)

<400> 1

gatctcaagg caaggactgc caccaccatc tggaacctgc cagcatatgc cttaggctcc 60

agca atg aat gcc cac tcc aag gag atg gtg ccc ctc atg ggc aaa aga 109

Met Asn Ala His Ser Lys Glu Met Val Pro Leu Met Gly Lys Arg

1 5 10 15

acc acg gca cct ggc ggg aac cct gtt gta ctg aca gag aag agg cca 157

Thr Thr Ala Pro Gly Gly Asn Pro Val Val Leu Thr Glu Lys Arg Pro

20 25 30

gca gat ctc acc ccc acc aag aag agt gca cac ttc ttc ctg gag ata 205

Ala Asp Leu Thr Pro Thr Lys Lys Ser Ala His Phe Phe Leu Glu Ile

35 40 45

gaa gga ttt gag ccc aac ccc acg gtc acc aag acc tct cca ccc atc 253

Glu Gly Phe Glu Pro Asn Pro Thr Val Thr Lys Thr Ser Pro Pro Ile

50 55 60

ttc tcc aag ccg atg gac tcc aac atc cgg cag tgc ctc tct ggc aac 301

Phe Ser Lys Pro Met Asp Ser Asn Ile Arg Gln Cys Leu Ser Gly Asn

65 70 75

tgt Cys 80	gat Asp	gac Asp	atg Met	gac Asp	tct Ser 85	ccc Pro	cag Gln	tct Ser	cct Pro	cag Gln 90	gat Asp	gat Asp	gtg Val	aca Thr	gag Glu 95	349
acc Thr	cca Pro	tcc Ser	aat Asn	ccc Pro 100	aac Asn	agt Ser	ccg Pro	agc Ser	gca Ala 105	aac Asn	ctg Leu	gcc Ala	aag Lys	gaa Glu 110	gaa Glu	397
cag Gln	agg Arg	cag Gln	aag Lys 115	aag Lys	aag Lys	cga Arg	ctg Leu	aag Lys 120	aag Lys	cgc Arg	atc Ile	ttc Phe	gcg Ala 125	gct Ala	gtg Val	445
tcc Ser	gag Glu 130	ggc Gly	tgc Cys	gtg Val	gag Glu	gag Glu	ctg Leu 135	cgg Arg	gaa Glu	ctc Leu	cta Leu	cag Gln 140	gat Asp	ctg Leu	cag Gln	493
gac Asp 145	ctc Leu	tgc Cys	agg Arg	agg Arg	cgc Arg 150	cgc Arg	ggc Gly	ctg Leu	gat Asp	gtg Val	cct Pro 155	gac Asp	ttc Phe	ctc Leu	atg Met	541
cac His 160	aag Lys	ctg Leu	aca Thr	gcc Ala 165	tca Ser 165	gac Asp	acc Thr	ggg Gly	aag Lys	acc Thr 170	tgc Cys	ctg Leu	atg Met	aag Lys	gct Ala 175	589
ttg Leu	ctc Leu	aac Asn	atc Ile	aat Asn 180	ccc Pro	aac Asn	acc Thr	aaa Lys	gag Glu 185	atc Ile	gtg Val	cgg Arg	att Ile	ctg Leu 190	ctt Leu	637
gcc Ala	ttc Phe	gct Ala	gag Glu 195	gag Glu	aac Asn	gac Asp	atc Ile	ctg Leu 200	gac Asp	agg Arg	ttc Phe	atc Ile	aac Asn 205	gct Ala	gag Glu	685
tac Tyr	acg Thr	gaa Glu 210	gag Glu	gcc Ala	tat Tyr	gaa Glu	ggg Gly 215	cag Gln	aca Thr	gcg Ala	ctg Leu	aac Asn 220	atc Ile	gcc Ala	atc Ile	733
gag Glu 225	cgg Arg	cgc Arg	cag Gln	gga Gly	gac Asp	atc Ile 230	aca Thr	gca Ala	gtg Val	ctt Leu	ata Ile 235	gca Ala	gcg Ala	ggt Gly	gct Ala	781
gac Asp 240	gtc Val	aat Asn	gct Ala	cac His	gcc Ala 245	aag Lys	ggg Gly	gtc Val	ttc Phe	ttc Phe 250	aac Asn	ccc Pro	aaa Lys	tac Tyr	cag Gln 255	829
cat His	gaa Glu	ggc Gly	ttc Phe	tat Tyr 260	ttt Phe	ggc Gly	gag Glu	aca Thr	ccc Pro 265	ctg Leu	gct Ala	ttg Leu	gca Ala	gcg Ala	tgt Cys 270	877
act Thr	aac Asn	cag Gln	cct Pro 275	gag Glu	att Ile	gtg Val	cag Gln	ctg Leu 280	ctg Leu	atg Met	gag Glu	aat Asn	gag Glu 285	cag Gln	aca Thr	925
gac Asp	atc Ile	act Thr 290	tcc Ser	cag Gln	gat Asp	tcc Ser	cgg Arg 295	gga Gly	aac Asn	aac Asn	atc Ile	ctg Leu 300	cac His	gcg Ala	ctg Leu	973
gtg Val 305	aca Thr	gtg Val	gct Ala	gag Glu	gac Asp	ttc Phe 310	aag Lys	act Thr	cag Gln	aat Asn	gac Asp 315	ttc Phe	gtt Val	aag Lys	cgc Arg	1021
atg Met 320	tat Tyr	gac Asp	atg Met	atc Ile	ctg Leu 325	ctg Leu	agg Arg	agt Ser	ggc Gly 330	aac Asn	tgg Trp	gag Glu	ctg Leu	gag Glu	acc Thr 335	1069
atg Met	cgc Arg	aac Asn	aac Asn	gat Asp 340	ggg Gly	ctc Leu	aca Thr	cca Pro	ctg Leu 345	cag Gln	ctg Leu	gct Ala	gcc Ala	aag Lys	atg Met 350	1117

ggc aag gct gag atc ctg aag tac atc ctc agc cgc gag atc aag gag	1165
Gly Lys Ala Glu Ile Leu Lys Tyr Ile Leu Ser Arg Glu Ile Lys Glu	
355 360 365	
aag cct ctc cgg agc ttg tcc agg aag ttc acg gac tgg gcg tat ggg	1213
Lys Pro Leu Arg Ser Leu Ser Arg Lys Phe Thr Asp Trp Ala Tyr Gly	
370 375 380	
cct gtg tca tcc tca ctc tat gac ctc acc aat gta gac aca acg acg	1261
Pro Val Ser Ser Ser Leu Tyr Asp Leu Thr Asn Val Asp Thr Thr Thr	
385 390 395	
gat aac tct gtg ctg gaa atc atc gtc tac aac acc aac att gat aac	1309
Asp Asn Ser Val Leu Glu Ile Ile Val Tyr Asn Thr Asn Ile Asp Asn	
400 405 410 415	
cga cat gag atg ctg acc ctg gag cct ctg cat acg ctg cta cac acg	1357
Arg His Glu Met Leu Thr Leu Glu Pro Leu His Thr Leu Leu His Thr	
420 425 430	
aaa tgg aag aaa ttt gcc aag tac atg ttc ttc ttg tcc ttc tgc ttc	1405
Lys Trp Lys Lys Phe Ala Lys Tyr Met Phe Phe Leu Ser Phe Cys Phe	
435 440 445	
tat ttc ttc tac aac atc acc ctg acc ctt gtc tct tac tac cgt cct	1453
Tyr Phe Phe Tyr Asn Ile Thr Leu Thr Leu Val Ser Tyr Tyr Arg Pro	
450 455 460	
cgg gaa gat gag gat ctc cca cac ccc ttg gcc ctg aca cac aaa atg	1501
Arg Glu Asp Glu Asp Leu Pro His Pro Leu Ala Leu Thr His Lys Met	
465 470 475	
agt tgg ctt cag ctc cta ggg agg atg ttt gtc ctc atc tgg gcc aca	1549
Ser Trp Leu Gln Leu Leu Gly Arg Met Phe Val Leu Ile Trp Ala Thr	
480 485 490 495	
tgc atc tct gtg aaa gaa ggc att gcc att ttc ctg ctg aga ccc tcc	1597
Cys Ile Ser Val Lys Glu Gly Ile Ala Ile Phe Leu Leu Arg Pro Ser	
500 505 510	
gat ctt cag tcc atc ctg tca gat gcc tgg ttt cac ttt gtc ttt ttt	1645
Asp Leu Gln Ser Ile Leu Ser Asp Ala Trp Phe His Phe Val Phe Phe	
515 520 525	
gtc caa gct gta ctt gtg ata ctg tct gta ttc ttg tac ttg ttt gcc	1693
Val Gln Ala Val Leu Val Ile Leu Ser Val Phe Leu Tyr Leu Phe Ala	
530 535 540	
tac aaa gaa tac ctc gcc tgc ctc gtg ctg gcc atg gcc ctg ggc tgg	1741
Tyr Lys Glu Tyr Leu Ala Cys Leu Val Leu Ala Met Ala Leu Gly Trp	
545 550 555	
gcg aac atg ctc tac tac acg aga ggc ttc cag tct atg ggc atg tac	1789
Ala Asn Met Leu Tyr Tyr Thr Arg Gly Phe Gln Ser Met Gly Met Tyr	
560 565 570 575	
agc gtc atg atc cag aag gtc att ttg cat gat gtc ctc aag ttc ttg	1837
Ser Val Met Ile Gln Lys Val Ile Leu His Asp Val Leu Lys Phe Leu	
580 585 590	
ttt gtt tac atc ctg ttc tta ctt gga ttt gga gta gcg ctg gcc tca	1885
Phe Val Tyr Ile Leu Phe Leu Leu Gly Phe Gly Val Ala Leu Ala Ser	
595 600 605	
ctg att gag aag tgc tcc aag gac aaa aag gac tgc agt tcc tat ggc	1933
Leu Ile Glu Lys Cys Ser Lys Asp Lys Lys Asp Cys Ser Ser Tyr Gly	
610 615 620	

4/75

agc ttc agc gac gcg gtg ctg gag ctc ttc aag ctc acc ata ggc ctg 1981
 Ser Phe Ser Asp Ala Val Leu Glu Leu Phe Lys Leu Thr Ile Gly Leu
 625 630 635

ggc gac ctg aac atc cag cag aac tcc acc tac ccc atc ctc ttt ctc 2029
 Gly Asp Leu Asn Ile Gln Gln Asn Ser Thr Tyr Pro Ile Leu Phe Leu
 640 645 650 655

ttc cta ctc atc acc tat gtc atc ctc acc ttc gtc ctc ctc ctc aac 2077
 Phe Leu Leu Ile Thr Tyr Val Ile Leu Thr Phe Val Leu Leu Leu Asn
 660 665 670

atg ctc atc gcc ctg atg ggg gag acg gtg gag aac gtc tcc aaa gaa 2125
 Met Leu Ile Leu Met Gly Glu Thr Val Glu Asn Val Ser Lys Glu
 675 680 685

agt gag cgg atc tgg cgc ttg cag aga gcc agg acc atc ttg gag ttt 2173
 Ser Glu Arg Ile Trp Arg Leu Gln Arg Ala Arg Thr Ile Leu Glu Phe
 690 695 700

gag aaa atg tta cca gaa tgg ctg aga agc aga ttc cgc atg ggc gag 2221
 Glu Lys Met Leu Pro Glu Trp Leu Arg Ser Arg Phe Arg Met Gly Glu
 705 710 715

ctg tgc aaa gta gca gat gag gac ttc cgg ctg tgt ctg cgg atc aac 2269
 Leu Cys Lys Val Ala Asp Glu Asp Phe Arg Leu Cys Leu Arg Ile Asn
 720 725 730 735

gag gtg aag tgg acg gaa tgg aaa aca cac gtg tcc ttc ctt aat gaa 2317
 Glu Val Lys Trp Thr Glu Trp Lys Thr His Val Ser Phe Leu Asn Glu
 740 745 750

gac ccg gga ccc ata aga cgg aca gca gat tta aac aag att caa gat 2365
 Asp Pro Gly Pro Ile Arg Arg Thr Ala Asp Leu Asn Lys Ile Gln Asp
 755 760 765

tct tcc agg agc aat agc aaa acc acc ctc tat gcg ttt gat gaa tta 2413
 Ser Ser Arg Ser Asn Ser Lys Thr Thr Leu Tyr Ala Phe Asp Glu Leu
 770 775 780

gat gaa ttc cca gaa acg tcg gtg tag 2440
 Asp Glu Phe Pro Glu Thr Ser Val *
 785 790

<210> 2

<211> 791

<212> PRT

<213> Mus musculus

<400> 2

Met Asn Ala His Ser Lys Glu Met Val Pro Leu Met Gly Lys Arg Thr
 1 5 10 15
 Thr Ala Pro Gly Gly Asn Pro Val Val Leu Thr Glu Lys Arg Pro Ala
 20 25 30
 Asp Leu Thr Pro Thr Lys Lys Ser Ala His Phe Phe Leu Glu Ile Glu
 35 40 45
 Gly Phe Glu Pro Asn Pro Thr Val Thr Lys Thr Ser Pro Pro Ile Phe
 50 55 60
 Ser Lys Pro Met Asp Ser Asn Ile Arg Gln Cys Leu Ser Gly Asn Cys
 65 70 75 80
 Asp Asp Met Asp Ser Pro Gln Ser Pro Gln Asp Asp Val Thr Glu Thr
 85 90 95
 Pro Ser Asn Pro Asn Ser Pro Ser Ala Asn Leu Ala Lys Glu Glu
 100 105 110
 Arg Gln Lys Lys Lys Arg Leu Lys Lys Arg Ile Phe Ala Ala Val Ser
 115 120 125
 Glu Gly Cys Val Glu Glu Leu Arg Glu Leu Leu Gln Asp Leu Gln Asp


```

      675      680      685
Glu Arg Ile Trp Arg Leu Gln Arg Ala Arg Thr Ile Leu Glu Phe Glu
      690      695      700
Lys Met Leu Pro Glu Trp Leu Arg Ser Arg Phe Arg Met Gly Glu Leu
      705      710      715      720
Cys Lys Val Ala Asp Glu Asp Phe Arg Leu Cys Leu Arg Ile Asn Glu
      725      730      735
Val Lys Trp Thr Glu Trp Lys Thr His Val Ser Phe Leu Asn Glu Asp
      740      745      750
Pro Gly Pro Ile Arg Arg Thr Ala Asp Leu Asn Lys Ile Gln Asp Ser
      755      760      765
Ser Arg Ser Asn Ser Lys Thr Thr Leu Tyr Ala Phe Asp Glu Leu Asp
      770      775      780
Glu Phe Pro Glu Thr Ser Val
      785      790

```

<210> 3

<211> 2373

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (1)...(2373)

<223> Generic sequence that encompasses all nucleotide sequences that encode mouse TRPV3 having an amino acid sequence as shown in SEQ ID NO:2

<221> misc_feature

<222> 15,120,180,195,210,231,255,264,294,306,312,384,495,873,882,984,1086,1116,1122,1155,1158,1161,1206,1332,1377,1440,1494,1533,1545,1554,1608,1713,1728,1821,1839,1860,1863,1872,1878,1941,2055,2064,2139,2241,2304,2307,2313,2370

<223> n = A,C,G, or T if after TC;
n = T or C if after AG

<221> misc_feature

<222> 45,90,339,354,366,408,441,444,447,450,564,606,675,678,885,957,981,1011,1089,1113,1125,1248,1386,1392,1461,1527,1701,2070,2079,2088,2094,2136,2142,2148,2187,2199,2271,2274,2310

<223> n = A,C,G, or T if after CG;
n = A or G if after AG

<221> misc_feature

<222> all "n" not specified above

<223> n = A,T,C or G

<400> 3

```

atg aay gcn cay wsn aar gar atg gtn ccn ytn atg ggn aar mgn acn      48
Met Asn Ala His Ser Lys Glu Met Val Pro Leu Met Gly Lys Arg Thr
  1              5              10              15

acn gcn ccn ggn ggn aay ccn gtn gtn ytn acn gar aar mgn ccn gcn      96
Thr Ala Pro Gly Gly Asn Pro Val Val Leu Thr Glu Lys Arg Pro Ala
              20              25              30

gay ytn acn ccn acn aar aar wsn gcn cay tty tty ytn gar ath gar      144
Asp Leu Thr Pro Thr Lys Lys Ser Ala His Phe Phe Leu Glu Ile Glu
      35              40              45

ggn tty gar ccn aay ccn acn gtn acn aar acn wsn ccn ccn ath tty      192
Gly Phe Glu Pro Asn Pro Thr Val Thr Lys Thr Ser Pro Pro Ile Phe
      50              55              60

wsn aar ccn atg gay wsn aay ath mgn car tgy ytn wsn ggn aay tgy      240
Ser Lys Pro Met Asp Ser Asn Ile Arg Gln Cys Leu Ser Gly Asn Cys

```

7/75

65	70					75					80					
gay Asp	gay Asp	atg Met	gay Asp	wsn Ser	ccn Pro	car Gln	wsn Ser	ccn Pro	car Gln	gay Asp	gay Asp	gtn Val	acn Thr	gar Glu	acn Thr	288
				85					90					95		
ccn Pro	wsn Ser	aay Asn	ccn Pro	aay Asn	wsn Ser	ccn Pro	wsn Ser	gcn Ala	aay Asn	ytn Leu	gcn Ala	aar Lys	gar Glu	gar Glu	car Gln	336
			100					105					110			
mgn Arg	car Gln	aar Lys	aar Lys	aar Lys	mgn Arg	ytn Leu	aar Lys	aar Lys	mgn Arg	ath Ile	tty Phe	gcn Ala	gcn Ala	gtn Val	wsn Ser	384
		115					120					125				
gar Glu	ggn Gly	tgy Cys	gtn Val	gar Glu	gar Glu	ytn Leu	mgn Arg	gar Glu	ytn Leu	ytn Leu	car Gln	gay Asp	ytn Leu	car Gln	gay Asp	432
	130					135					140					
ytn Leu	tgy Cys	mgn Arg	mgn Arg	mgn Arg	mgn Arg	ggn Gly	ytn Leu	gay Asp	gtn Val	ccn Pro	gay Asp	tty Phe	ytn Leu	atg Met	cay His	480
145					150					155					160	
aar Lys	ytn Leu	acn Thr	gcn Ala	wsn Ser	gay Asp	acn Thr	ggn Gly	aar Lys	acn Thr	tgy Cys	ytn Leu	atg Met	aar Lys	gcn Ala	ytn Leu	528
				165					170					175		
ytn Leu	aay Asn	ath Ile	aay Asn	ccn Pro	aay Asn	acn Thr	aar Lys	gar Glu	ath Ile	gtn Val	mgn Arg	ath Ile	ytn Leu	ytn Leu	gcn Ala	576
			180					185					190			
tty Phe	gcn Ala	gar Glu	gar Glu	aay Asn	gay Asp	ath Ile	ytn Leu	gay Asp	mgn Arg	tty Phe	ath Ile	aay Asn	gcn Ala	gar Glu	tay Tyr	624
		195					200					205				
acn Thr	gar Glu	gar Glu	gcn Ala	tay Tyr	gar Glu	ggn Gly	car Gln	acn Thr	gcn Ala	ytn Leu	aay Asn	ath Ile	gcn Ala	ath Ile	gar Glu	672
	210					215					220					
mgn Arg	mgn Arg	car Gln	ggn Gly	gay Asp	ath Ile	acn Thr	gcn Ala	gtn Val	ytn Leu	ath Ile	gcn Ala	gcn Ala	ggn Gly	gcn Ala	gay Asp	720
225				230					235						240	
gtn Val	aay Asn	gcn Ala	cay His	gcn Ala	aar Lys	ggn Gly	gtn Val	tty Phe	tty Phe	aay Asn	ccn Pro	aar Lys	tay Tyr	car Gln	cay His	768
				245				250						255		
gar Glu	ggn Gly	tty Phe	tay Tyr	tty Phe	ggn Gly	gar Glu	acn Thr	ccn Pro	ytn Leu	gcn Ala	ytn Leu	gcn Ala	gcn Ala	tgy Cys	acn Thr	816
			260					265					270			
aay Asn	car Gln	ccn Pro	gar Glu	ath Ile	gtn Val	car Gln	ytn Leu	ytn Leu	atg Met	gar Glu	aay Asn	gar Glu	car Gln	acn Thr	gay Asp	864
		275					280					285				
ath Ile	acn Thr	wsn Ser	car Gln	gay Asp	wsn Ser	mgn Arg	ggn Gly	aay Asn	aay Asn	ath Ile	ytn Leu	cay His	gcn Ala	ytn Leu	gtn Val	912
						295					300					
acn Thr	gtn Val	gcn Ala	gar Glu	gay Asp	tty Phe	aar Lys	acn Thr	car Gln	aay Asn	gay Asp	tty Phe	gtn Val	aar Lys	mgn Arg	atg Met	960
	305				310					315					320	
tay Tyr	gay Asp	atg Met	ath Ile	ytn Leu	ytn Leu	mgn Arg	wsn Ser	ggn Gly	aay Asn	tgg Trp	gar Glu	ytn Leu	gar Glu	acn Thr	atg Met	1008
				325				330						335		
mgn Arg	aay Asn	aay Asn	gay Asp	ggn Gly	ytn Leu	acn Thr	ccn Pro	ytn Leu	car Gln	ytn Leu	gcn Ala	gcn Ala	aar Lys	atg Met	ggn Gly	1056

340							345					350					
aar Lys	gcn Ala	gar Glu 355	ath Ile	ytn Leu	aar Lys	tay Tyr	ath Ile 360	ytn Leu	wsn Ser	mgn Arg	gar Glu	ath Ile 365	aar Lys	gar Glu	aar Lys	1104	
ccn Pro	ytn Leu 370	mgn Arg	wsn Ser	ytn Leu	wsn Ser	mgn Arg 375	aar Lys	tty Phe	acn Thr	gay Asp	tgg Trp 380	gcn Ala	tay Tyr	ggn Gly	ccn Pro	1152	
gtn Val 385	wsn Ser	wsn Ser	wsn Ser	ytn Leu	tay Tyr 390	gay Asp	ytn Leu	acn Thr	aay Asn	gtn Val 395	gay Asp	acn Thr	acn Thr	acn Thr	gay Asp 400	1200	
aay Asn	wsn Ser	gtn Val	ytn Leu	gar Glu 405	ath Ile	ath Ile	gtn Val	tay Tyr	aay Asn 410	acn Thr	aay Asn	ath Ile	gay Asp	aay Asn 415	mgn Arg	1248	
cay His	gar Glu	atg Met	ytn Leu 420	acn Thr	ytn Leu	gar Glu	ccn Pro	ytn Leu 425	cay His	acn Thr	ytn Leu	ytn Leu	cay His 430	acn Thr	aar Lys	1296	
tgg Trp	aar Lys	aar Lys 435	tty Phe	gcn Ala	aar Lys	tay Tyr	atg Met 440	tty Phe	tty Phe	ytn Leu	wsn Ser	tty Phe 445	tgy Cys	tty Phe	tay Tyr	1344	
tty Phe 450	tty Phe	tay Tyr	aay Asn	ath Ile	acn Thr	ytn Leu 455	acn Thr	ytn Leu	gtn Val	wsn Ser	tay Tyr 460	tay Tyr	mgn Arg	ccn Pro	mgn Arg	1392	
gar Glu 465	gay Asp	gar Glu	gay Asp	ytn Leu	ccn Pro 470	cay His	ccn Pro	ytn Leu	gcn Ala	ytn Leu 475	acn Thr	cay His	aar Lys	atg Met	wsn Ser 480	1440	
tgg Trp	ytn Leu	car Gln	ytn Leu 485	ytn Leu	ggn Gly	mgn Arg	atg Met	tty Phe	gtn Val 490	ytn Leu	ath Ile	tgg Trp	gcn Ala	acn Thr 495	tgy Cys	1488	
ath Ile	wsn Ser	gtn Val	aar Lys 500	gar Glu	ggn Gly	ath Ile	gcn Ala	ath Ile 505	tty Phe	ytn Leu	ytn Leu	mgn Arg	ccn Pro 510	wsn Ser	gay Asp	1536	
ytn Leu	car Gln	wsn Ser 515	ath Ile	ytn Leu	wsn Ser	gay Asp	gcn Ala 520	tgg Trp	tty Phe	cay His	tty Phe	gtn Val 525	tty Phe	tty Phe	gtn Val	1584	
car Gln 530	gcn Ala	gtn Val	ytn Leu	gtn Val	ath Ile	ytn Leu 535	wsn Ser	gtn Val	tty Phe	ytn Leu	tay Tyr 540	ytn Leu	tty Phe	gcn Ala	tay Tyr	1632	
aar Lys 545	gar Glu	tay Tyr	ytn Leu	gcn Ala	tgy Cys 550	ytn Leu	gtn Val	ytn Leu	gcn Ala	atg Met 555	gcn Ala	ytn Leu	ggn Gly	tgg Trp	gcn Ala 560	1680	
aay Asn	atg Met	ytn Leu	tay Tyr	tay Tyr 565	acn Thr	mgn Arg	ggn Gly	tty Phe	car Gln 570	wsn Ser	atg Met	ggn Gly	atg Met	tay Tyr 575	wsn Ser	1728	
gtn Val	atg Met	ath Ile	car Gln 580	aar Lys	gtn Val	ath Ile	ytn Leu	cay His 585	gay Asp	gtn Val	ytn Leu	aar Lys	tty Phe 590	ytn Leu	tty Phe	1776	
gtn Val	tay Tyr	ath Ile	ytn Leu	tty Phe	ytn Leu	ytn Leu	ggn Gly 600	tty Phe	ggn Gly	gtn Val	gcn Ala	ytn Leu 605	gcn Ala	wsn Ser	ytn Leu	1824	
ath Ile	gar Glu	aar Lys	tgy Cys	wsn Ser	aar Lys	gay Asp	aar Lys	aar Lys	gay Asp	tgy Cys	wsn Ser	wsn Ser	tay Tyr	ggn Gly	wsn Ser	1872	

9/75

610	615	620	
tty wsn gay gcn gtn ytn gar ytn tty aar ytn acn ath ggn ytn ggn Phe Ser Asp Ala Val Leu Glu Leu Phe Lys Leu Thr Ile Gly Leu Gly 625 630 635 640			1920
gay ytn aay ath car car aay wsn acn tay ccn ath ytn tty ytn tty Asp Leu Asn Ile Gln Asn Ser Thr Tyr Pro Ile Leu Phe Leu Phe 645 650 655			1968
ytn ytn ath acn tay gtn ath ytn acn tty gtn ytn ytn ytn aay atg Leu Leu Ile Thr Tyr Val Ile Leu Thr Phe Val Leu Leu Leu Asn Met 660 665 670			2016
ytn ath gcn ytn atg ggn gar acn gtn gar aay gtn wsn aar gar wsn Leu Ile Ala Leu Met Gly Glu Thr Val Glu Asn Val Ser Lys Glu Ser 675 680 685			2064
gar mgn ath tgg mgn ytn car mgn gcn mgn acn ath ytn gar tty gar Glu Arg Ile Trp Arg Leu Gln Arg Ala Arg Thr Ile Leu Glu Phe Glu 690 695 700			2112
aar atg ytn ccn gar tgg ytn mgn wsn mgn tty mgn atg ggn gar ytn Lys Met Leu Pro Glu Trp Leu Arg Ser Arg Phe Arg Met Gly Glu Leu 705 710 715 720			2160
tgy aar gtn gcn gay gar gay tty mgn ytn tgy ytn mgn ath aay gar Cys Lys Val Ala Asp Glu Asp Phe Arg Leu Cys Leu Arg Ile Asn Glu 725 730 735			2208
gtn aar tgg acn gar tgg aar acn cay gtn wsn tty ytn aay gar gay Val Lys Trp Thr Glu Trp Lys Thr His Val Ser Phe Leu Asn Glu Asp 740 745 750			2256
ccn ggn ccn ath mgn mgn acn gcn gay ytn aay aar ath car gay wsn Pro Gly Pro Ile Arg Arg Thr Ala Asp Leu Asn Lys Ile Gln Asp Ser 755 760 765			2304
wsn mgn wsn aay wsn aar acn acn ytn tay gcn tty gay gar ytn gay Ser Arg Ser Asn Ser Lys Thr Thr Leu Tyr Ala Phe Asp Glu Leu Asp 770 775 780			2352
gar tty ccn gar acn wsn gtn Glu Phe Pro Glu Thr Ser Val 785 790			2373
<210> 4			
<211> 2432			
<212> DNA			
<213> Human			
<220>			
<221> CDS			
<222> (57)... (2432)			
<400> 4			
gacatgcggt gatctcaggg caagggttgc caccgaccacc cagaacctca ccagcc atg			59
			Met
			1
aaa gcc cac ccc aag gag atg gtg cct ctc atg ggc aag aga gtt gct			
Lys Ala His Pro Lys Glu Met Val Pro Leu Met Gly Lys Arg Val Ala			107
5 10 15			
gcc ccc agt ggg aac cct gcc gtc ctg cca gag aag agg ccg gcg gag			
Ala Pro Ser Gly Asn Pro Ala Val Leu Pro Glu Lys Arg Pro Ala Glu			155
20 25 30			

atc Ile	acc Thr	ccc Pro	aca Thr	aag Lys	aag Lys	agt Ser	gca Ala	cac His	ttc Phe	ttc Phe	ctg Leu	gag Glu	ata Ile	gaa Glu	ggg Gly	203
	35					40					45					
ttt Phe	gaa Glu	ccc Pro	aac Asn	ccc Pro	aca Thr	gtt Val	gcc Ala	aag Lys	acc Thr	tct Ser	cct Pro	cct Pro	gtc Val	ttc Phe	tcc Ser	251
50					55					60					65	
aag Lys	ccc Pro	atg Met	gat Asp	tcc Ser	aac Asn	atc Ile	cgg Arg	cag Gln	tgc Cys	atc Ile	tct Ser	ggg Gly	aac Asn	tgt Cys	gat Asp	299
				70					75					80		
gac Asp	atg Met	gac Asp	tcc Ser	ccc Pro	cag Gln	tct Ser	cct Pro	cag Gln	gat Asp	gat Asp	gtg Val	aca Thr	gag Glu	acc Thr	cca Pro	347
			85					90					95			
tcc Ser	aat Asn	ccc Pro	aac Asn	agc Ser	ccc Pro	agt Ser	gca Ala	cag Gln	ctg Leu	gcc Ala	aag Lys	gaa Glu	gag Glu	cag Gln	agg Arg	395
		100					105					110				
agg Arg	aaa Lys	aag Lys	agg Arg	cgg Arg	ctg Leu	aag Lys	aag Lys	cgc Arg	atc Ile	ttt Phe	gca Ala	gcc Ala	gtg Val	tct Ser	gag Glu	443
	115				120						125					
ggc Gly	tgc Cys	gtg Val	gag Glu	gag Glu	ttg Leu	gta Val	gag Glu	ttg Leu	ctg Leu	gtg Val	gag Glu	ctg Leu	cag Gln	gag Glu	ctt Leu	491
130					135					140					145	
tgc Cys	agg Arg	cgg Arg	cgc Arg	cat His	gat Asp	gag Glu	gat Asp	gtg Val	cct Pro	gac Asp	ttc Phe	ctc Leu	atg Met	cac His	aag Lys	539
				150					155					160		
ctg Leu	acg Thr	gcc Ala	tcc Ser	gac Asp	acg Thr	ggg Gly	aag Lys	acc Thr	tgc Cys	ctg Leu	atg Met	aag Lys	gcc Ala	ttg Leu	tta Leu	587
			165					170					175			
aac Asn	atc Ile	aac Asn	ccc Pro	aac Asn	acc Thr	aag Lys	gag Glu	ata Ile	gtg Val	cgg Arg	atc Ile	ctg Leu	ctt Leu	gcc Ala	ttt Phe	635
		180					185					190				
gct Ala	gaa Glu	gag Glu	aac Asn	gac Asp	atc Ile	ctg Leu	ggc Gly	agg Arg	ttc Phe	atc Ile	aac Asn	gcc Ala	gag Glu	tac Tyr	aca Thr	683
	195					200					205					
gag Glu	gag Glu	gcc Ala	tat Tyr	gaa Glu	ggg Gly	cag Gln	acg Thr	gcg Ala	ctg Leu	aac Asn	atc Ile	gcc Ala	atc Ile	gag Glu	cgg Arg	731
210					215					220					225	
cgg Arg	cag Gln	ggg Gly	gac Asp	atc Ile	gca Ala	gcc Ala	ctg Leu	ctc Leu	atc Ile	gcc Ala	gcc Ala	ggc Gly	gcc Ala	gac Asp	gtc Val	779
				230					235					240		
aac Asn	gcg Ala	cac His	gcc Ala	aag Lys	ggg Gly	gcc Ala	ttc Phe	ttc Phe	aac Asn	ccc Pro	aag Lys	tac Tyr	caa Gln	cac His	gaa Glu	827
			245					250					255			
ggc Gly	ttc Phe	tac Tyr	ttc Phe	ggg Gly	gag Glu	acg Thr	ccc Pro	ctg Leu	gcc Ala	ctg Leu	gca Ala	gca Ala	tgc Cys	acc Thr	aac Asn	875
		260					265				270					
cag Gln	ccc Pro	gag Glu	att Ile	gtg Val	cag Gln	ctg Leu	ctg Leu	atg Met	gag Glu	cac His	gag Glu	cag Gln	acg Thr	gac Asp	atc Ile	923
	275					280					285					
acc Thr	tgc Ser	cgg Arg	gac Asp	tca Ser	cga Arg	ggc Gly	aac Asn	aac Asn	atc Ile	ctt Leu	cac His	gcc Ala	ctg Leu	gtg Val	acc Thr	971
290					295					300					305	

gtg gcc gag gac ttc aag acg cag aat gac ttt gtg aag cgc atg tac	1019
Val Ala Glu Asp Phe Lys Thr Gln Asn Asp Phe Val Lys Arg Met Tyr	
310 315 320	
gac atg atc cta ctg cgg agt ggc aac tgg gag ctg gag acc act cgc	1067
Asp Met Ile Leu Leu Arg Ser Gly Asn Trp Glu Leu Glu Thr Thr Arg	
325 330 335	
aac aac gat ggc ctc acg ccg ctg cag ctg gcc gcc aag atg ggc aag	1115
Asn Asn Asp Gly Leu Thr Pro Leu Gln Leu Ala Ala Lys Met Gly Lys	
340 345 350	
gcg gag atc ctg aag tac atc ctc agt cgt gag atc aag gag aag cgg	1163
Ala Glu Ile Leu Lys Tyr Ile Leu Ser Arg Glu Ile Lys Glu Lys Arg	
355 360 365	
ctc cgg agc ctg tcc agg aag ttc acc gac tgg gcg tac gga ccc gtg	1211
Leu Arg Ser Leu Ser Arg Lys Phe Thr Asp Trp Ala Tyr Gly Pro Val	
370 375 380 385	
tca tcc tcc ctc tac gac ctc acc aac gtg gac acc acc acg gac aac	1259
Ser Ser Ser Leu Tyr Asp Leu Thr Asn Val Asp Thr Thr Thr Asp Asn	
390 395 400	
tca gtg ctg gaa atc act gtc tac aac acc aac atc gac aac cgg cat	1307
Ser Val Leu Glu Ile Thr Val Tyr Asn Thr Asn Ile Asp Asn Arg His	
405 410 415	
gag atg ctg acc ctg gag ccg ctg cac acg ctg ctg cat atg aag tgg	1355
Glu Met Leu Thr Leu Glu Pro Leu His Thr Leu Leu His Met Lys Trp	
420 425 430	
aag aag ttt gcc aag cac atg ttc ttt ctg tcc ttc tgc ttt tat ttc	1403
Lys Lys Phe Ala Lys His Met Phe Phe Leu Ser Phe Phe Cys Phe Tyr Phe	
435 440 445	
ttc tac aac atc acc ctg acc ctc gtc tgc tac tac cgc ccc cgg gag	1451
Phe Tyr Asn Ile Thr Leu Thr Leu Val Ser Tyr Tyr Arg Pro Arg Glu	
450 455 460 465	
gag gag gcc atc ccg cac ccc ttg gcc ctg acg cac aag atg ggg tgg	1499
Glu Glu Ala Ile Pro His Pro Leu Ala Leu Thr His Lys Met Gly Trp	
470 475 480	
ctg cag ctc cta ggg agg atg ttt gtg ctc atc tgg gcc atg tgc atc	1547
Leu Gln Leu Leu Gly Arg Met Phe Val Leu Ile Trp Ala Met Cys Ile	
485 490 495	
tct gtg aaa gag ggc att gcc atc ttc ctg ctg aga ccc tcg gat ctg	1595
Ser Val Lys Glu Gly Ile Ala Ile Phe Leu Leu Arg Pro Ser Asp Leu	
500 505 510	
cag tcc atc ctc tcg gat gcc tgg ttc cac ttt gtc ttt ttt atc caa	1643
Gln Ser Ile Leu Ser Asp Ala Trp Phe His Phe Val Phe Phe Ile Gln	
515 520 525	
gct gtg ctt gtg ata ctg tct gtc ttc ttg tac ttg ttt gcc tac aaa	1691
Ala Val Leu Val Ile Leu Ser Val Phe Leu Tyr Leu Phe Ala Tyr Lys	
530 535 540 545	
gag tac ctc gcc tgc ctc gtg ctg gcc atg gcc ctg ggc tgg gcg aac	1739
Glu Tyr Leu Ala Cys Leu Val Leu Ala Met Ala Leu Gly Trp Ala Asn	
550 555 560	
atg ctc tac tat acg cgg ggt ttc cag tcc atg ggc atg tac agc gtc	1787
Met Leu Tyr Tyr Thr Arg Gly Phe Gln Ser Met Gly Met Tyr Ser Val	
565 570 575	

12/75

atg atc cag aag gtc att ttg cat gat gtt ctg aag ttc ttg ttt gta	1835
Met Ile Gln Lys Val Ile Leu His Asp Val Leu Lys Phe Leu Phe Val	
580 585 590	
tat atc gtg ttt ttg ctt gga ttt gga gta gcc ttg gcc tcg ctg atc	1883
Tyr Ile Val Phe Leu Leu Gly Phe Gly Val Ala Leu Ala Ser Leu Ile	
595 600 605	
gag aag tgt ccc aaa gac aac aag gac tgc agc tcc tac ggc agc ttc	1931
Glu Lys Cys Pro Lys Asp Asn Lys Asp Cys Ser Ser Tyr Gly Ser Phe	
610 615 620 625	
agc gac gca gtg ctg gaa ctc ttc aag ctc acc ata ggc ctg ggt gac	1979
Ser Asp Ala Val Leu Glu Leu Phe Lys Leu Thr Ile Gly Leu Gly Asp	
630 635 640	
ctg aac atc cag cag aac tcc aag tat ccc att ctc ttt ctg ttc ctg	2027
Leu Asn Ile Gln Gln Asn Ser Lys Tyr Pro Ile Leu Phe Leu Phe Leu	
645 650 655	
ctc atc acc tat gtc atc ctc acc ttt gtt ctc ctc ctc aac atg ctc	2075
Leu Ile Thr Tyr Val Ile Leu Thr Phe Val Leu Leu Leu Asn Met Leu	
660 665 670	
att gct ctg atg ggc gag act gtg gag aac gtc tcc aag gag agc gaa	2123
Ile Ala Leu Met Gly Glu Thr Val Glu Asn Val Ser Lys Glu Ser Glu	
675 680 685	
cgc atc tgg cgc ctg cag aga gcc agg acc atc ttg gag ttt gag aaa	2171
Arg Ile Trp Arg Leu Gln Arg Ala Arg Thr Ile Leu Glu Phe Glu Lys	
690 695 700 705	
atg tta cca gaa tgg ctg agg agc aga ttc cgg atg gga gag ctg tgc	2219
Met Leu Pro Glu Trp Leu Arg Ser Arg Phe Arg Met Gly Glu Leu Cys	
710 715 720	
aaa gtg gcc gag gat gat ttc cga ctg tgt ttg cgg atc aat gag gtg	2267
Lys Val Ala Glu Asp Asp Phe Arg Leu Cys Leu Arg Ile Asn Glu Val	
725 730 735	
aag tgg act gaa tgg aag acg cac gtc tcc ttc ctt aac gaa gac ccg	2315
Lys Trp Thr Glu Trp Lys Thr His Val Ser Phe Leu Asn Glu Asp Pro	
740 745 750	
ggg cct gta aga cga aca gca gat ttc aac aaa atc caa gat tct tcc	2363
Gly Pro Val Arg Arg Thr Ala Asp Phe Asn Lys Ile Gln Asp Ser Ser	
755 760 765	
agg aac aac agc aaa acc act ctc aat gca ttt gaa gaa gtc gag gaa	2411
Arg Asn Asn Ser Lys Thr Thr Leu Asn Ala Phe Glu Glu Val Glu Glu	
770 775 780 785	
ttc ccg gaa acc tcg gtg tag	2432
Phe Pro Glu Thr Ser Val *	
790	

<210> 5
 <211> 791
 <212> PRT
 <213> Human

<400> 5
 Met Lys Ala His Pro Lys Glu Met Val Pro Leu Met Gly Lys Arg Val
 1 5 10 15
 Ala Ala Pro Ser Gly Asn Pro Ala Val Leu Pro Glu Lys Arg Pro Ala
 20 25 30

13/75

Glu	Ile	Thr	Pro	Thr	Lys	Lys	Ser	Ala	His	Phe	Phe	Leu	Glu	Ile	Glu
		35					40					45			
Gly	Phe	Glu	Pro	Asn	Pro	Thr	Val	Ala	Lys	Thr	Ser	Pro	Pro	Val	Phe
	50					55					60				
Ser	Lys	Pro	Met	Asp	Ser	Asn	Ile	Arg	Gln	Cys	Ile	Ser	Gly	Asn	Cys
65				70						75				80	
Asp	Asp	Met	Asp	Ser	Pro	Gln	Ser	Pro	Gln	Asp	Asp	Val	Thr	Glu	Thr
				85					90				95		
Pro	Ser	Asn	Pro	Asn	Ser	Pro	Ser	Ala	Gln	Leu	Ala	Lys	Glu	Glu	Gln
			100					105					110		
Arg	Arg	Lys	Lys	Arg	Arg	Leu	Lys	Lys	Arg	Ile	Phe	Ala	Ala	Val	Ser
		115					120					125			
Glu	Gly	Cys	Val	Glu	Glu	Leu	Val	Glu	Leu	Leu	Val	Glu	Leu	Gln	Glu
	130					135					140				
Leu	Cys	Arg	Arg	Arg	His	Asp	Glu	Asp	Val	Pro	Asp	Phe	Leu	Met	His
145					150					155					160
Lys	Leu	Thr	Ala	Ser	Asp	Thr	Gly	Lys	Thr	Cys	Leu	Met	Lys	Ala	Leu
				165					170					175	
Leu	Asn	Ile	Asn	Pro	Asn	Thr	Lys	Glu	Ile	Val	Arg	Ile	Leu	Leu	Ala
			180					185					190		
Phe	Ala	Glu	Glu	Asn	Asp	Ile	Leu	Gly	Arg	Phe	Ile	Asn	Ala	Glu	Tyr
	195						200					205			
Thr	Glu	Glu	Ala	Tyr	Glu	Gly	Gln	Thr	Ala	Leu	Asn	Ile	Ala	Ile	Glu
	210					215						220			
Arg	Arg	Gln	Gly	Asp	Ile	Ala	Ala	Leu	Leu	Ile	Ala	Ala	Gly	Ala	Asp
225				230						235					240
Val	Asn	Ala	His	Ala	Lys	Gly	Ala	Phe	Phe	Asn	Pro	Lys	Tyr	Gln	His
				245					250					255	
Glu	Gly	Phe	Tyr	Phe	Gly	Glu	Thr	Pro	Leu	Ala	Leu	Ala	Ala	Cys	Thr
			260					265					270		
Asn	Gln	Pro	Glu	Ile	Val	Gln	Leu	Leu	Met	Glu	His	Glu	Gln	Thr	Asp
		275					280					285			
Ile	Thr	Ser	Arg	Asp	Ser	Arg	Gly	Asn	Asn	Ile	Leu	His	Ala	Leu	Val
	290					295					300				
Thr	Val	Ala	Glu	Asp	Phe	Lys	Thr	Gln	Asn	Asp	Phe	Val	Lys	Arg	Met
305				310						315					320
Tyr	Asp	Met	Ile	Leu	Arg	Ser	Gly	Asn	Trp	Glu	Leu	Glu	Thr	Thr	
				325				330					335		
Arg	Asn	Asn	Asp	Gly	Leu	Thr	Pro	Leu	Gln	Leu	Ala	Ala	Lys	Met	Gly
			340					345					350		
Lys	Ala	Glu	Ile	Leu	Lys	Tyr	Ile	Leu	Ser	Arg	Glu	Ile	Lys	Glu	Lys
		355					360					365			
Arg	Leu	Arg	Ser	Leu	Ser	Arg	Lys	Phe	Thr	Asp	Trp	Ala	Tyr	Gly	Pro
	370					375					380				
Val	Ser	Ser	Ser	Leu	Tyr	Asp	Leu	Thr	Asn	Val	Asp	Thr	Thr	Thr	Asp
385					390					395					400
Asn	Ser	Val	Leu	Glu	Ile	Thr	Val	Tyr	Asn	Thr	Asn	Ile	Asp	Asn	Arg
				405					410					415	
His	Glu	Met	Leu	Thr	Leu	Glu	Pro	Leu	His	Thr	Leu	Leu	His	Met	Lys
			420					425					430		
Trp	Lys	Lys	Phe	Ala	Lys	His	Met	Phe	Phe	Leu	Ser	Phe	Cys	Phe	Tyr
		435					440					445			
Phe	Phe	Tyr	Asn	Ile	Thr	Leu	Thr	Leu	Val	Ser	Tyr	Tyr	Arg	Pro	Arg
	450					455					460				
Glu	Glu	Glu	Ala	Ile	Pro	His	Pro	Leu	Ala	Leu	Thr	His	Lys	Met	Gly
465					470					475					480
Trp	Leu	Gln	Leu	Leu	Gly	Arg	Met	Phe	Val	Leu	Ile	Trp	Ala	Met	Cys
				485					490					495	
Ile	Ser	Val	Lys	Glu	Gly	Ile	Ala	Ile	Phe	Leu	Leu	Arg	Pro	Ser	Asp
			500					505					510		
Leu	Gln	Ser	Ile	Leu	Ser	Asp	Ala	Trp	Phe	His	Phe	Val	Phe	Phe	Ile
		515					520					525			
Gln	Ala	Val	Leu	Val	Ile	Leu	Ser	Val	Phe	Leu	Tyr	Leu	Phe	Ala	Tyr
	530					535					540				
Lys	Glu	Tyr	Leu	Ala	Cys	Leu	Val	Leu	Ala	Met	Ala	Leu	Gly	Trp	Ala
545					550					555					560
Asn	Met	Leu	Tyr	Tyr	Thr	Arg	Gly	Phe	Gln	Ser	Met	Gly	Met	Tyr	Ser
				565					570					575	

14/75

```

Val Met Ile Gln Lys Val Ile Leu His Asp Val Leu Lys Phe Leu Phe
      580      585      590
Val Tyr Ile Val Phe Leu Leu Gly Phe Gly Val Ala Leu Ala Ser Leu
      595      600      605
Ile Glu Lys Cys Pro Lys Asp Asn Lys Asp Cys Ser Ser Tyr Gly Ser
      610      615      620
Phe Ser Asp Ala Val Leu Glu Leu Phe Lys Leu Thr Ile Gly Leu Gly
      625      630      635      640
Asp Leu Asn Ile Gln Gln Asn Ser Lys Tyr Pro Ile Leu Phe Leu Phe
      645      650      655
Leu Leu Ile Thr Tyr Val Ile Leu Thr Phe Val Leu Leu Leu Asn Met
      660      665      670
Leu Ile Ala Leu Met Gly Glu Thr Val Glu Asn Val Ser Lys Glu Ser
      675      680      685
Glu Arg Ile Trp Arg Leu Gln Arg Ala Arg Thr Ile Leu Glu Phe Glu
      690      695      700
Lys Met Leu Pro Glu Trp Leu Arg Ser Arg Phe Arg Met Gly Glu Leu
      705      710      715      720
Cys Lys Val Ala Glu Asp Asp Phe Arg Leu Cys Leu Arg Ile Asn Glu
      725      730      735
Val Lys Trp Thr Glu Trp Lys Thr His Val Ser Phe Leu Asn Glu Asp
      740      745      750
Pro Gly Pro Val Arg Arg Thr Ala Asp Phe Asn Lys Ile Gln Asp Ser
      755      760      765
Ser Arg Asn Asn Ser Lys Thr Thr Leu Asn Ala Phe Glu Glu Val Glu
      770      775      780
Glu Phe Pro Glu Thr Ser Val
      785      790

```

<210> 6

<211> 2373

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (1)... (2373)

<223> Generic sequence that encompasses all nucleotide sequences that encode human TRPV3 having an amino acid sequence as shown in SEQ ID NO:5

<221> misc_feature

<222> 60,120,180,195,210,231,255,264,294,306,312,384,495,873,882,984,1086,1116,1122,1158,1161,1164,1206,1332,1377,1494,1533,1545,1554,1608,1713,1728,1821,1860,1863,1872,1878,1944,2055,2064,2139,2241,2304,2307,2319,2370

<223> n = A,T,C or G if after TC;
n = T or C if after AG

<221> misc_feature

<222> 45,90,219,339,342,351,354,366,441,444,447,564,606,675,678,876,885,957,981,1011,1089,1107,1113,1125,1248,1386,1392,1461,1527,1701,2070,2079,2088,2136,2142,2148,2187,2199,2271,2274,2310

<223> n = A,T,C or G if after CG;
n = A or G if after AG

<221> misc_feature

<222> all "n" not specified above

<223> n = A,T,C or G

<400> 6

```

atg aar gcn cay ccn aar gar atg gtn ccn ytn atg ggn aar mgn gtn
Met Lys Ala His Pro Lys Glu Met Val Pro Leu Met Gly Lys Arg Val
  1              5              10              15

```

48

15/75

gcn gcn ccn wsn ggn aay ccn gcn gtn ytn ccn gar aar mgn ccn gcn	96
Ala Ala Pro Ser Gly Asn Pro Ala Val Leu Pro Glu Lys Arg Pro Ala	
20 25 30	
gar ath acn ccn acn aar aar wsn gcn cay tty tty ytn gar ath gar	144
Glu Ile Thr Pro Thr Lys Lys Ser Ala His Phe Phe Leu Glu Ile Glu	
35 40 45	
ggn tty gar ccn aay ccn acn gtn gcn aar acn wsn ccn ccn gtn tty	192
Gly Phe Glu Pro Asn Pro Thr Val Ala Lys Thr Ser Pro Pro Val Phe	
50 55 60	
wsn aar ccn atg gay wsn aay ath mgn car tgy ath wsn ggn aay tgy	240
Ser Lys Pro Met Asp Ser Asn Ile Arg Gln Cys Ile Ser Gly Asn Cys	
65 70 75 80	
gay gay atg gay wsn ccn car wsn ccn car gay gay gtn acn gar acn	288
Asp Asp Met Asp Ser Pro Gln Ser Pro Gln Asp Asp Val Thr Glu Thr	
85 90 95	
ccn wsn aay ccn aay wsn ccn wsn gcn car ytn gcn aar gar gar car	336
Pro Ser Asn Pro Asn Ser Pro Ser Ala Gln Leu Ala Lys Glu Glu Gln	
100 105 110	
mgn mgn aar aar mgn mgn ytn aar aar mgn ath tty gcn gcn gtn wsn	384
Arg Arg Lys Lys Arg Arg Leu Lys Lys Arg Ile Phe Ala Ala Val Ser	
115 120 125	
gar ggn tgy gtn gar gar ytn gtn gar ytn ytn gtn gar ytn car gar	432
Glu Gly Cys Val Glu Glu Leu Val Glu Leu Leu Val Glu Leu Gln Glu	
130 135 140	
ytn tgy mgn mgn mgn cay gay gar gay gtn ccn gay tty ytn atg cay	480
Leu Cys Arg Arg Arg His Asp Glu Asp Val Pro Asp Phe Leu Met His	
145 150 155 160	
aar ytn acn gcn wsn gay acn ggn aar acn tgy ytn atg aar gcn ytn	528
Lys Leu Thr Ala Ser Asp Thr Gly Lys Thr Cys Leu Met Lys Ala Leu	
165 170 175	
ytn aay ath aay ccn aay acn aar gar ath gtn mgn ath ytn ytn gcn	576
Leu Asn Ile Asn Pro Asn Thr Lys Glu Ile Val Arg Ile Leu Leu Ala	
180 185 190	
tty gcn gar gar aay gay ath ytn ggn mgn tty ath aay gcn gar tay	624
Phe Ala Glu Glu Asn Asp Ile Leu Gly Arg Phe Ile Asn Ala Glu Tyr	
195 200 205	
acn gar gar gcn tay gar ggn car acn gcn ytn aay ath gcn ath gar	672
Thr Glu Glu Ala Tyr Glu Gly Gln Thr Ala Leu Asn Ile Ala Ile Glu	
210 215 220	
mgn mgn car ggn gay ath gcn gcn ytn ytn ath gcn gcn ggn gcn gay	720
Arg Arg Gln Gly Asp Ile Ala Ala Leu Leu Ile Ala Ala Gly Ala Asp	
225 230 235 240	
gtn aay gcn cay gcn aar ggn gcn tty tty aay ccn aar tay car cay	768
Val Asn Ala His Ala Lys Gly Ala Phe Phe Asn Pro Lys Tyr Gln His	
245 250 255	
gar ggn tty tay tty ggn gar acn ccn ytn gcn ytn gcn gcn tgy acn	816
Glu Gly Phe Tyr Phe Gly Glu Thr Pro Leu Ala Leu Ala Ala Cys Thr	
260 265 270	
aay car ccn gar ath gtn car ytn ytn atg gar cay gar car acn gay	864
Asn Gln Pro Glu Ile Val Gln Leu Leu Met Glu His Glu Gln Thr Asp	
275 280 285	

16/75

ath Ile 290	acn Thr	wsn Ser	mgn Arg	gay Asp	wsn Ser	mgn Arg	ggn Gly	aay Asn	aay Asn	ath Ile	ytn Leu	cay His	gcn Ala	ytn Leu	gtn Val	912
acn Thr 305	gtn Val	gcn Ala	gar Glu	gay Asp	tty Phe	aar Lys	acn Thr	car Gln	aay Asn	gay Asp	tty Phe	gtn Val	aar Lys	mgn Arg	atg Met	960
tay Tyr	gay Asp	atg Met	ath Ile	ytn Leu	ytn Leu	mgn Arg	wsn Ser	ggn Gly	aay Asn	tgg Trp	gar Glu	ytn Leu	gar Glu	acn Thr	acn Thr	1008
mgn Arg	aay Asn	aay Asn	gay Asp	ggn Gly	ytn Leu	acn Thr	ccn Pro	ytn Leu	car Gln	ytn Leu	gcn Ala	gcn Ala	aar Lys	atg Met	ggn Gly	1056
aar Lys	gcn Ala	gar Glu	ath Ile	ytn Leu	aar Lys	tay Tyr	ath Ile	ytn Leu	wsn Ser	mgn Arg	gar Glu	ath Ile	aar Lys	gar Glu	aar Lys	1104
mgn Arg	ytn Leu	mgn Arg	wsn Ser	ytn Leu	wsn Ser	mgn Arg	aar Lys	tty Phe	acn Thr	gay Asp	tgg Trp	gcn Ala	tay Tyr	ggn Gly	ccn Pro	1152
gtn Val 385	wsn Ser	wsn Ser	wsn Ser	ytn Leu	tay Tyr	gay Asp	ytn Leu	acn Thr	aay Asn	gtn Val	gay Asp	acn Thr	acn Thr	acn Thr	gay Asp	1200
aay Asn	wsn Ser	gtn Val	ytn Leu	gar Glu	ath Ile	acn Thr	gtn Val	tay Tyr	aay Asn	acn Thr	aay Asn	ath Ile	gay Asp	aay Asn	mgn Arg	1248
cay His	gar Glu	atg Met	ytn Leu	acn Thr	ytn Leu	gar Glu	ccn Pro	ytn Leu	cay His	acn Thr	ytn Leu	ytn Leu	cay His	atg Met	aar Lys	1296
tgg Trp	aar Lys	aar Lys	tty Phe	gcn Ala	aar Lys	cay His	atg Met	tty Phe	tty Phe	ytn Leu	wsn Ser	tty Phe	tgy Cys	tty Phe	tay Tyr	1344
tty Phe	tty Phe	tay Tyr	aay Asn	ath Ile	acn Thr	ytn Leu	acn Thr	ytn Leu	gtn Val	wsn Ser	tay Tyr	tay Tyr	mgn Arg	ccn Pro	mgn Arg	1392
gar Glu 465	gar Glu	gar Glu	gcn Ala	ath Ile	ccn Pro	cay His	ccn Pro	ytn Leu	gcn Ala	ytn Leu	acn Thr	cay His	aar Lys	atg Met	ggn Gly	1440
tgg Trp	ytn Leu	car Gln	ytn Leu	ytn Leu	ggn Gly	mgn Arg	atg Met	tty Phe	gtn Val	ytn Leu	ath Ile	tgg Trp	gcn Ala	atg Met	tgy Cys	1488
ath Ile	wsn Ser	gtn Val	aar Lys	gar Glu	ggn Gly	ath Ile	gcn Ala	ath Ile	tty Phe	ytn Leu	ytn Leu	mgn Arg	ccn Pro	wsn Ser	gay Asp	1536
ytn Leu	car Gln	wsn Ser	ath Ile	ytn Leu	wsn Ser	gay Asp	gcn Ala	tgg Trp	tty Phe	cay His	tty Phe	gtn Val	tty Phe	tty Phe	ath Ile	1584
car Gln	gcn Ala	gtn Val	ytn Leu	gtn Val	ath Ile	ytn Leu	wsn Ser	gtn Val	tty Phe	ytn Leu	tay Tyr	ytn Leu	tty Phe	gcn Ala	tay Tyr	1632
aar Lys	gar Glu	tay Tyr	ytn Leu	gcn Ala	tgy Cys	ytn Leu	gtn Val	ytn Leu	gcn Ala	atg Met	gcn Ala	ytn Leu	ggn Gly	tgg Trp	gcn Ala	1680

17/75

aay atg ytn tay tay acn mgn ggn tty car wsn atg ggn atg tay wsn Asn Met Leu Tyr Tyr Thr Arg Gly Phe Gln Ser Met Gly Met Tyr Ser 565 570 575	1728
gtn atg ath car aar gtn ath ytn cay gay gtn ytn aar tty ytn tty Val Met Ile Gln Lys Val Ile Leu His Asp Val Leu Lys Phe Leu Phe 580 585 590	1776
gtn tay ath gtn tty ytn ytn ggn tty ggn gtn gcn ytn gcn wsn ytn Val Tyr Ile Val Phe Leu Leu Gly Phe Gly Val Ala Leu Ala Ser Leu 595 600 605	1824
ath gar aar tgy ccn aar gay aay aar gay tgy wsn wsn tay ggn wsn Ile Glu Lys Cys Pro Lys Asp Asn Lys Asp Cys Ser Ser Tyr Gly Ser 610 615 620	1872
tty wsn gay gcn gtn ytn gar ytn tty aar ytn acn ath ggn ytn ggn Phe Ser Asp Ala Val Leu Glu Leu Phe Lys Leu Thr Ile Gly Leu Gly 625 630 635 640	1920
gay ytn aay ath car car aay wsn aar tay ccn ath ytn tty ytn tty Asp Leu Asn Ile Gln Gln Asn Ser Lys Tyr Pro Ile Leu Phe Leu Phe 645 650 655	1968
ytn ytn ath acn tay gtn ath ytn acn tty gtn ytn ytn ytn aay atg Leu Leu Ile Thr Tyr Val Ile Leu Thr Phe Val Leu Leu Leu Asn Met 660 665 670	2016
ytn ath gcn ytn atg ggn gar acn gtn gar aay gtn wsn aar gar wsn Leu Ile Ala Leu Met Gly Glu Thr Val Glu Asn Val Ser Lys Glu Ser 675 680 685	2064
gar mgn ath tgg mgn ytn car mgn gcn mgn acn ath ytn gar tty gar Glu Arg Ile Trp Arg Leu Gln Arg Ala Arg Thr Ile Leu Glu Phe Glu 690 695 700	2112
aar atg ytn ccn gar tgg ytn mgn wsn mgn tty mgn atg ggn gar ytn Lys Met Leu Pro Glu Trp Leu Arg Ser Arg Phe Arg Met Gly Glu Leu 705 710 715 720	2160
tgy aar gtn gcn gar gay gay tty mgn ytn tgy ytn mgn ath aay gar Cys Lys Val Ala Glu Asp Asp Phe Arg Leu Cys Leu Arg Ile Asn Glu 725 730 735	2208
gtn aar tgg acn gar tgg aar acn cay gtn wsn tty ytn aay gar gay Val Lys Trp Thr Glu Trp Lys Thr His Val Ser Phe Leu Asn Glu Asp 740 745 750	2256
ccn ggn ccn gtn mgn mgn acn gcn gay tty aay aar ath car gay wsn Pro Gly Pro Val Arg Arg Thr Ala Asp Phe Asn Lys Ile Gln Asp Ser 755 760 765	2304
wsn mgn aay aay wsn aar acn acn ytn aay gcn tty gar gar gtn gar Ser Arg Asn Asn Ser Lys Thr Thr Leu Asn Ala Phe Glu Glu Val Glu 770 775 780	2352
gar tty ccn gar acn wsn gtn Glu Phe Pro Glu Thr Ser Val 785 790	2373

<210> 7

<211> 4113

<212> DNA

<213> Mus musculus

<220>

<221> CDS

<222> (448) ... (3762)

<400> 7

```

ggtgaaacta ctctgctggg agaacctagg aggcagtgaa gcctcatacc tcagcatcca 60
cgagacttct tcacttttcc tgggcatcta tgggtgtaat atggaggtaa tatctatgga 120
ggtttttgtgt ttggattcct tgcttctctt gaagattctt gctggctcca gtgcagatca 180
aggggaagaga agcctggatt tttctggctc catttagaga agcttagtgc aggagacggg 240
gctgggctgg gctgtgtgtg actataaagt cctccctcct ccagtgaagt aagagacaag 300
caggctcttt gaggagagag aagctcttgg ctgattgagc agctccacgt cctggctgtc 360
ccggagcttg atacatagaa aagactgacc tcagatacac agagatcctt ctgcttctgt 420
ctcccaagtg ctgggatcac aggcaag atg tcc ttc gag gga gcc agg ctc agc 474
Met Ser Phe Glu Gly Ala Arg Leu Ser
1 5

atg agg agc cgc aga aat ggt act atg ggc agc acc cgg acc ctg tac 522
Met Arg Ser Arg Arg Asn Gly Thr Met Gly Ser Thr Arg Thr Leu Tyr
10 15 20 25

tcc agt gta tct cgg agc aca gac gtg tcc tac agt gac agt gat ttg 570
Ser Ser Val Ser Arg Ser Thr Asp Val Ser Tyr Ser Asp Ser Asp Leu
30 35 40

gtg aat ttt att cag gca aat ttt aaa aaa cga gaa tgt gtc ttc ttt 618
Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
45 50 55

acc aga gac tcc aag gcc atg gag aac ata tgc aag tgt ggt tat gcc 666
Thr Arg Asp Ser Lys Ala Met Glu Asn Ile Cys Lys Cys Gly Tyr Ala
60 65 70

cag agc cag cac atc gaa ggc acc cag atc aac caa aat gag aag tgg 714
Gln Ser Gln His Ile Glu Gly Thr Gln Ile Asn Gln Asn Glu Lys Trp
75 80 85

aac tac aaa aaa cat acc aag gag ttt cca aca gac gcc ttc ggg gac 762
Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
90 95 100 105

att cag ttt gag act ctg ggg aag aaa ggc aag tac tta cgc ttg tcc 810
Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Leu Arg Leu Ser
110 115 120

tgt gac acc gac tct gaa act ctc tac gaa ctg ctg acc cag cac tgg 858
Cys Asp Thr Asp Ser Glu Thr Leu Tyr Glu Leu Leu Thr Gln His Trp
125 130 135

cac ctc aaa aca ccc aac ctg gtc att tca gtg acg ggt gga gcc aaa 906
His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys
140 145 150

aac ttt gct ttg aag cca cgc atg cgc aag atc ttc agc agg ctg att 954
Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile
155 160 165

tac atc gca cag tct aaa ggt gcg tgg att ctc act gga ggc act cac 1002
Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His
170 175 180 185

tac ggc ctg atg aag tac ata ggc gag gtg gtg aga gac aac acc atc 1050
Tyr Gly Leu Met Lys Tyr Ile Gly Glu Val Arg Asp Asn Thr Ile
190 195 200

agc agg aac tca gaa gag aac atc gtg gcc att ggc atc gca gca tgg 1098
Ser Arg Asn Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp
205 210 215

ggc atg gtc tcc aac agg gac acc ctc atc agg agc tgt gat gat gag 1146
Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Ser Cys Asp Asp Glu

```


220	225	230	
gga cat ttt tca gct caa tac atc atg gat gac ttt acc aga gac cct Gly His Phe Ser Ala Gln Tyr Ile Met Asp Asp Phe Thr Arg Asp Pro 235 240 245			1194
cta tac atc ctg gac aac aac cat acc cac ctg ctg ctt gtg gac aac Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn 250 255 260 265			1242
ggt tgt cat gga cac ccc aca gtg gaa gcc aag ctc cgg aat cag ctg Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu 270 275 280			1290
gaa aag tac atc tct gag cgc acc agt caa gat tcc aac tat ggt ggt Glu Lys Tyr Ile Ser Glu Arg Thr Ser Gln Asp Ser Asn Tyr Gly Gly 285 290 295			1338
aag atc ccc atc gtg tgt ttt gcc caa gga ggt gga aga gag act cta Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Arg Glu Thr Leu 300 305 310			1386
aaa gcc atc aac acc tct gtc aaa agc aag atc cct tgt gtg gtg gtg Lys Ala Ile Asn Thr Ser Val Lys Ser Lys Ile Pro Cys Val Val Val 315 320 325			1434
gaa ggc tcg ggg cag att gct gat gtg atc gcc agc ctg gtg gag gtg Glu Gly Ser Gly Gln Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val 330 335 340 345			1482
gag gat gtt tta acc tct tcc atg gtc aaa gag aag ctg gta cgc ttt Glu Asp Val Leu Thr Ser Ser Met Val Lys Glu Lys Leu Val Arg Phe 350 355 360			1530
tta cca cgc act gtg tcc cgg ctg cct gaa gag gaa att gag agc tgg Leu Pro Arg Thr Val Ser Arg Leu Pro Glu Glu Glu Ile Glu Ser Trp 365 370 375			1578
atc aaa tgg ctc aaa gaa att ctt gag agt tct cac cta ctc aca gta Ile Lys Trp Leu Lys Glu Ile Leu Glu Ser Ser His Leu Leu Thr Val 380 385 390			1626
att aag atg gaa gag gct gga gat gag att gtg agc aac gcc att tcc Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser 395 400 405			1674
tat gcg ctg tac aaa gcc ttc agc act aat gag caa gac aag gac aac Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Asn Glu Gln Asp Lys Asp Asn 410 415 420 425			1722
tgg aat gga cag ctg aag ctt ctg ctg gag tgg aac cag ttg gac ctt Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu 430 435 440			1770
gcc agt gat gag atc ttc acc aat gac cgc cgc tgg gag tct gcc gac Ala Ser Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp 445 450 455			1818
ctt cag gag gtc atg ttc acg gct ctc ata aag gac aga ccc aag ttt Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe 460 465 470			1866
gtc cgc ctc ttt ctg gag aat ggc ctg aat ctg cag aag ttt ctc acc Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Gln Lys Phe Leu Thr 475 480 485			1914
aat gaa gtc ctc aca gag ctc ttc tcc acc cac ttc agc acc cta gtg Asn Glu Val Leu Thr Glu Leu Phe Ser Thr His Phe Ser Thr Leu Val 490 495			1962

20/75

490	495	500	505	
tac cgg aac ctg cag atc gcc aag aac tcc tac aat gac gca ctc ctc				2010
Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu	510	515	520	
acc ttt gtc tgg aag ttg gtg gca aac ttc cgt cga agc ttc tgg aaa				2058
Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Ser Phe Trp Lys	525	530	535	
gag gac aga agc agc agg gag gac ttg gat gtg gaa ctc cat gat gca				2106
Glu Asp Arg Ser Ser Arg Glu Asp Leu Asp Val Glu Leu His Asp Ala	540	545	550	
tct ctc acc acc cgg cac ccg ctg caa gct ctc ttc atc tgg gcc att				2154
Ser Leu Thr Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile	555	560	565	
ctt cag aac aag aag gaa ctc tcc aag gtc att tgg gag cag acc aaa				2202
Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Lys	570	575	580	585
ggc tgt act ctg gca gcc ttg ggg gcc agc aag ctt ctg aag acc ctg				2250
Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu	590	595	600	
gcc aaa gtt aag aat gat atc aac gct gct ggg gaa tcg gag gaa ctg				2298
Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu	605	610	615	
gcc aat gaa tat gag acc cga gca gtg gag ttg ttc acc gag tgt tac				2346
Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr	620	625	630	
agc aat gat gaa gac ttg gca gaa cag cta ctg gtc tac tcc tgc gaa				2394
Ser Asn Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu	635	640	645	
gcc tgg ggt ggg agc aac tgt ctg gag ctg gca gtg gag gct aca gat				2442
Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp	650	655	660	665
cag cat ttc atc gct cag cct ggg gtc cag aat ttc ctt tct aag caa				2490
Gln His Phe Ile Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln	670	675	680	
tgg tat gga gag att tcc cga gac acg aag aac tgg aag att atc ctg				2538
Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu	685	690	695	
tgt cta ttc att atc ccc tta gtg ggc tgt ggc ctc gta tca ttt agg				2586
Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Leu Val Ser Phe Arg	700	705	710	
aag aaa ccc att gac aag cac aag aag ctg ctg tgg tac tat gtg gcc				2634
Lys Lys Pro Ile Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala	715	720	725	
ttc ttc acg tcg ccc ttc gtg gtc ttc tcc tgg aac gtg gtc ttc tac				2682
Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr	730	735	740	745
atc gcc ttc ctc ctg ctg ttt gcc tat gtg ctg ctc atg gac ttc cac				2730
Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His	750	755	760	
tca gtg cca cac acc ccc gag ctg atc ctc tac gcc ctg gtc ttc gtc				2778
Ser Val Pro His Thr Pro Glu Leu Ile Leu Tyr Ala Leu Val Phe Val				

21/75

765							770					775					
ctc	ttc	tgt	gat	gaa	gtg	agg	cag	tgg	tac	atg	aac	gga	gtg	aat	tat	2826	
Leu	Phe	Cys	Asp	Glu	Val	Arg	Gln	Trp	Tyr	Met	Asn	Gly	Val	Asn	Tyr		
		780					785					790					
ttc	acc	gac	cta	tgg	aac	gtt	atg	gac	acc	ctg	gga	ctc	ttc	tac	ttc	2874	
Phe	Thr	Asp	Leu	Trp	Asn	Val	Met	Asp	Thr	Leu	Gly	Leu	Phe	Tyr	Phe		
	795					800					805						
ata	gcg	ggg	att	gta	ttc	cgg	ctc	cac	tct	tct	aat	aaa	agc	tcg	ttg	2922	
Ile	Ala	Gly	Ile	Val	Phe	Arg	Leu	His	Ser	Ser	Asn	Lys	Ser	Ser	Leu		
810					815					820					825		
tac	tct	ggg	cgc	gtc	att	ttc	tgt	ctg	gat	tac	att	ata	ttc	acg	cta	2970	
Tyr	Ser	Gly	Arg	Val	Ile	Phe	Cys	Leu	Asp	Tyr	Ile	Ile	Phe	Thr	Leu		
				830					835					840			
agg	ctc	atc	cac	att	ttc	acc	gtc	agc	agg	aac	ttg	gga	ccc	aag	att	3018	
Arg	Leu	Ile	His	Ile	Phe	Thr	Val	Ser	Arg	Asn	Leu	Gly	Pro	Lys	Ile		
			845					850					855				
ata	atg	ctg	cag	cgg	atg	ctg	atc	gac	gtt	ttc	ttc	ttc	ctg	ttc	ctc	3066	
Ile	Met	Leu	Gln	Arg	Met	Leu	Ile	Asp	Val	Phe	Phe	Phe	Leu	Phe	Leu		
		860					865					870					
ttt	gct	gtg	tgg	atg	gtg	gcc	ttt	ggc	gtg	gcc	aga	cag	ggg	atc	cta	3114	
Phe	Ala	Val	Trp	Met	Val	Ala	Phe	Gly	Val	Ala	Arg	Gln	Gly	Ile	Leu		
	875					880					885						
agg	caa	aat	gaa	cag	cgc	tgg	aga	tgg	atc	ttc	cgc	tct	gtc	atc	tat	3162	
Arg	Gln	Asn	Glu	Gln	Arg	Trp	Arg	Trp	Ile	Phe	Arg	Ser	Val	Ile	Tyr		
890					895					900					905		
gag	ccc	tac	ctg	gcc	atg	ttt	ggc	cag	gtt	ccc	agt	gac	gtg	gat	agt	3210	
Glu	Pro	Tyr	Leu	Ala	Met	Phe	Gly	Gln	Val	Pro	Ser	Asp	Val	Asp	Ser		
				910					915					920			
acc	aca	tat	gac	ttc	tcc	cac	tgt	acc	ttc	tcg	gga	aat	gag	tcc	aag	3258	
Thr	Thr	Tyr	Asp	Phe	Ser	His	Cys	Thr	Phe	Ser	Gly	Asn	Glu	Ser	Lys		
			925					930					935				
cca	ctg	tgt	gtg	gag	ctg	gat	gag	cac	aac	ctg	ccc	cgc	ttc	cct	gag	3306	
Pro	Leu	Cys	Val	Glu	Leu	Asp	Glu	His	Asn	Leu	Pro	Arg	Phe	Pro	Glu		
		940					945					950					
tgg	atc	acc	att	ccg	ctg	gtg	tgc	atc	tac	atg	ctc	tcc	acc	aat	atc	3354	
Trp	Ile	Thr	Ile	Pro	Leu	Val	Cys	Ile	Tyr	Met	Leu	Ser	Thr	Asn	Ile		
	955					960					965						
ctt	ctg	gtc	aac	ctc	ctg	gtc	gcc	atg	ttt	ggc	tac	acg	gta	ggc	att	3402	
Leu	Leu	Val	Asn	Leu	Leu	Val	Ala	Met	Phe	Gly	Tyr	Thr	Val	Gly	Ile		
970					975					980					985		
gta	cag	gag	aac	aac	gac	cag	gtc	tgg	aaa	ttc	cag	cgg	tac	ttc	ctg	3450	
Val	Gln	Glu	Asn	Asn	Asp	Gln	Val	Trp	Lys	Phe	Gln	Arg	Tyr	Phe	Leu		
				990					995					1000			
gtg	cag	gag	tac	tgc	aac	cgc	cta	aac	atc	ccc	ttc	ccc	ttc	gtt	gtc	3498	
Val	Gln	Glu	Tyr	Cys	Asn	Arg	Leu	Asn	Ile	Pro	Phe	Pro	Phe	Val	Val		
			1005					1010					1015				
ttc	gct	tat	ttc	tac	atg	gtg	gtg	aag	aag	tgt	ttc	aaa	tgc	tgc	tgt	3546	
Phe	Ala	Tyr	Phe	Tyr	Met	Val	Val	Lys	Lys	Cys	Phe	Lys	Cys	Cys	Cys		
		1020					1025					1030					
aaa	gag	aag	aat	atg	gag	tct	aat	gcc	tgc	tgt	ttc	aga	aat	gag	gac	3594	
Lys	Glu	Lys	Asn	Met	Glu	Ser	Asn	Ala	Cys	Cys	Phe	Arg	Asn	Glu	Asp		

22/75

1035	1040	1045	
aat gag act ttg gcg tgg gag ggt gtc atg aag gag aat tac ctt gtc			3642
Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val			
1050	1055	1060	1065
aag atc aac acg aaa gcc aac gac aac tca gag gag atg agg cat cgg			3690
Lys Ile Asn Thr Lys Ala Asn Asp Asn Ser Glu Glu Met Arg His Arg			
	1070	1075	1080
ttt aga caa ctg gac tca aag ctt aac gac ctc aaa agt ctt ctg aaa			3738
Phe Arg Gln Leu Asp Ser Lys Leu Asn Asp Leu Lys Ser Leu Leu Lys			
	1085	1090	1095
gag att gct aat aac atc aag taa ggctggcgat gcttggtgggg agaaacccaaa			3792
Glu Ile Ala Asn Asn Ile Lys *			
1100			
tcacaatgag gtcacagcaa ccccttggat gtggaggctc atgggacact gatggacagt			3852
actgctaatag acttctaaag gagacatttt cagggtccctg agcacagggt ggatgactct			3912
tagtcaccct caagggcata ggtcagggag caaagtgtac agaggacttt acacctgaag			3972
aggggtgcaa aggaccatgt tcttctgtga aggtgcctgt gtttctgca tctcagagcc			4032
ttgtcctgat gctgagggat taggtgttga cactcctttc ccacgactgt gactctggcc			4092
ctgattttat acttatactg c			4113
<210> 8			
<211> 1104			
<212> PRT			
<213> Mus musculus			
<400> 8			
Met Ser Phe Glu Gly Ala Arg Leu Ser Met Arg Ser Arg Arg Asn Gly			
1 5 10 15			
Thr Met Gly Ser Thr Arg Thr Leu Tyr Ser Ser Val Ser Arg Ser Thr			
20 25 30			
Asp Val Ser Tyr Ser Asp Ser Asp Leu Val Asn Phe Ile Gln Ala Asn			
35 40 45			
Phe Lys Lys Arg Glu Cys Val Phe Phe Thr Arg Asp Ser Lys Ala Met			
50 55 60			
Glu Asn Ile Cys Lys Cys Gly Tyr Ala Gln Ser Gln His Ile Glu Gly			
65 70 75 80			
Thr Gln Ile Asn Gln Asn Glu Lys Trp Asn Tyr Lys Lys His Thr Lys			
85 90 95			
Glu Phe Pro Thr Asp Ala Phe Gly Asp Ile Gln Phe Glu Thr Leu Gly			
100 105 110			
Lys Lys Gly Lys Tyr Leu Arg Leu Ser Cys Asp Thr Asp Ser Glu Thr			
115 120 125			
Leu Tyr Glu Leu Leu Thr Gln His Trp His Leu Lys Thr Pro Asn Leu			
130 135 140			
Val Ile Ser Val Thr Gly Gly Ala Lys Asn Phe Ala Leu Lys Pro Arg			
145 150 155 160			
Met Arg Lys Ile Phe Ser Arg Leu Ile Tyr Ile Ala Gln Ser Lys Gly			
165 170 175			
Ala Trp Ile Leu Thr Gly Gly Thr His Tyr Gly Leu Met Lys Tyr Ile			
180 185 190			
Gly Glu Val Val Arg Asp Asn Thr Ile Ser Arg Asn Ser Glu Glu Asn			
195 200 205			
Ile Val Ala Ile Gly Ile Ala Ala Trp Gly Met Val Ser Asn Arg Asp			
210 215 220			
Thr Leu Ile Arg Ser Cys Asp Asp Glu Gly His Phe Ser Ala Gln Tyr			
225 230 235 240			
Ile Met Asp Asp Phe Thr Arg Asp Pro Leu Tyr Ile Leu Asp Asn Asn			
245 250 255			
His Thr His Leu Leu Leu Val Asp Asn Gly Cys His Gly His Pro Thr			
260 265 270			
Val Glu Ala Lys Leu Arg Asn Gln Leu Glu Lys Tyr Ile Ser Glu Arg			
275 280 285			
Thr Ser Gln Asp Ser Asn Tyr Gly Gly Lys Ile Pro Ile Val Cys Phe			

290	295	300
Ala Gln Gly Gly Gly Arg Glu Thr Leu Lys Ala Ile Asn Thr Ser Val		
305	310	315
Lys Ser Lys Ile Pro Cys Val Val Val Glu Gly Ser Gly Gln Ile Ala		
	325	330
Asp Val Ile Ala Ser Leu Val Glu Val Glu Asp Val Leu Thr Ser Ser		
	340	345
Met Val Lys Glu Lys Leu Val Arg Phe Leu Pro Arg Thr Val Ser Arg		
	355	360
Leu Pro Glu Glu Glu Ile Glu Ser Trp Ile Lys Trp Leu Lys Glu Ile		
	370	375
Leu Glu Ser Ser His Leu Leu Thr Val Ile Lys Met Glu Glu Ala Gly		
385	390	395
Asp Glu Ile Val Ser Asn Ala Ile Ser Tyr Ala Leu Tyr Lys Ala Phe		
	405	410
Ser Thr Asn Glu Gln Asp Lys Asp Asn Trp Asn Gly Gln Leu Lys Leu		
	420	425
Leu Leu Glu Trp Asn Gln Leu Asp Leu Ala Ser Asp Glu Ile Phe Thr		
	435	440
Asn Asp Arg Arg Trp Glu Ser Ala Asp Leu Gln Glu Val Met Phe Thr		
	450	455
Ala Leu Ile Lys Asp Arg Pro Lys Phe Val Arg Leu Phe Leu Glu Asn		
465	470	475
Gly Leu Asn Leu Gln Lys Phe Leu Thr Asn Glu Val Leu Thr Glu Leu		
	485	490
Phe Ser Thr His Phe Ser Thr Leu Val Tyr Arg Asn Leu Gln Ile Ala		
	500	505
Lys Asn Ser Tyr Asn Asp Ala Leu Leu Thr Phe Val Trp Lys Leu Val		
	515	520
Ala Asn Phe Arg Arg Ser Phe Trp Lys Glu Asp Arg Ser Ser Arg Glu		
	530	535
Asp Leu Asp Val Glu Leu His Asp Ala Ser Leu Thr Thr Arg His Pro		
545	550	555
Leu Gln Ala Leu Phe Ile Trp Ala Ile Leu Gln Asn Lys Lys Glu Leu		
	565	570
Ser Lys Val Ile Trp Glu Gln Thr Lys Gly Cys Thr Leu Ala Ala Leu		
	580	585
Gly Ala Ser Lys Leu Leu Lys Thr Leu Ala Lys Val Lys Asn Asp Ile		
	595	600
Asn Ala Ala Gly Glu Ser Glu Glu Leu Ala Asn Glu Tyr Glu Thr Arg		
	610	615
Ala Val Glu Leu Phe Thr Glu Cys Tyr Ser Asn Asp Glu Asp Leu Ala		
625	630	635
Glu Gln Leu Leu Val Tyr Ser Cys Glu Ala Trp Gly Gly Ser Asn Cys		
	645	650
Leu Glu Leu Ala Val Glu Ala Thr Asp Gln His Phe Ile Ala Gln Pro		
	660	665
Gly Val Gln Asn Phe Leu Ser Lys Gln Trp Tyr Gly Glu Ile Ser Arg		
	675	680
Asp Thr Lys Asn Trp Lys Ile Leu Cys Leu Phe Ile Ile Pro Leu		
	690	695
Val Gly Cys Gly Leu Val Ser Phe Arg Lys Lys Pro Ile Asp Lys His		
705	710	715
Lys Lys Leu Leu Trp Tyr Tyr Val Ala Phe Thr Ser Pro Phe Val		
	725	730
Val Phe Ser Trp Asn Val Val Phe Tyr Ile Ala Phe Leu Leu Leu Phe		
	740	745
Ala Tyr Val Leu Leu Met Asp Phe His Ser Val Pro His Thr Pro Glu		
	755	760
Leu Ile Leu Tyr Ala Leu Val Phe Val Leu Phe Cys Asp Glu Val Arg		
	770	775
Gln Trp Tyr Met Asn Gly Val Asn Tyr Phe Thr Asp Leu Trp Asn Val		
785	790	795
Met Asp Thr Leu Gly Leu Phe Tyr Phe Ile Ala Gly Ile Val Phe Arg		
	805	810
Leu His Ser Ser Asn Lys Ser Ser Leu Tyr Ser Gly Arg Val Ile Phe		
	820	825
Cys Leu Asp Tyr Ile Ile Phe Thr Leu Arg Leu Ile His Ile Phe Thr		

24/75

835	840	845
Val Ser Arg Asn Leu Gly Pro Lys Ile Ile Met Leu Gln Arg Met Leu		
850	855	860
Ile Asp Val Phe Phe Phe Leu Phe Leu Phe Ala Val Trp Met Val Ala		
865	870	875
Phe Gly Val Ala Arg Gln Gly Ile Leu Arg Gln Asn Glu Gln Arg Trp		
885	890	895
Arg Trp Ile Phe Arg Ser Val Ile Tyr Glu Pro Tyr Leu Ala Met Phe		
900	905	910
Gly Gln Val Pro Ser Asp Val Asp Ser Thr Thr Tyr Asp Phe Ser His		
915	920	925
Cys Thr Phe Ser Gly Asn Glu Ser Lys Pro Leu Cys Val Glu Leu Asp		
930	935	940
Glu His Asn Leu Pro Arg Phe Pro Glu Trp Ile Thr Ile Pro Leu Val		
945	950	955
Cys Ile Tyr Met Leu Ser Thr Asn Ile Leu Leu Val Asn Leu Leu Val		
965	970	975
Ala Met Phe Gly Tyr Thr Val Gly Ile Val Gln Glu Asn Asn Asp Gln		
980	985	990
Val Trp Lys Phe Gln Arg Tyr Phe Leu Val Gln Glu Tyr Cys Asn Arg		
995	1000	1005
Leu Asn Ile Pro Phe Pro Phe Val Val Phe Ala Tyr Phe Tyr Met Val		
1010	1015	1020
Val Lys Lys Cys Phe Lys Cys Cys Cys Lys Glu Lys Asn Met Glu Ser		
1025	1030	1035
Asn Ala Cys Cys Phe Arg Asn Glu Asp Asn Glu Thr Leu Ala Trp Glu		
1045	1050	1055
Gly Val Met Lys Glu Asn Tyr Leu Val Lys Ile Asn Thr Lys Ala Asn		
1060	1065	1070
Asp Asn Ser Glu Glu Met Arg His Arg Phe Arg Gln Leu Asp Ser Lys		
1075	1080	1085
Leu Asn Asp Leu Lys Ser Leu Leu Lys Glu Ile Ala Asn Asn Ile Lys		
1090	1095	1100

<210> 9

<211> 3312

<212> DNA

<213> Artificial Sequence

<220>

<223> Generic sequence that encompasses all nucleotide sequences that encode mouse TRPM8 having an amino acid sequence as shown in SEQ ID NO:8

<221> CDS

<222> (1)...(3312)

<221> misc_feature

<222> 6,27,36,60,78,81,87,93,105,111,117,183,225,363,378,441,498,522,606,615,663,687,711,858,870,879,957,966,1053,1056,1101,1128,1161,1164,1215,1227,1251,1329,1365,1494,1506,1545,1602,1623,1626,1662,1731,1785,1842,1902,1941,1962,2037,2061,2133,2199,2217,2286,2457,2460,2469,2472,2481,2550,2706,2751,2763,2781,2796,2808,2898,3120,3225,3261,3282

<223> n = A,T,C or G if after TC;

n = T or C if after AG

<221> misc_feature

<222> 21,33,39,42,66,90,156,177,357,480,486,501,591,609,669,684,741,834,864,930,1080,1092,1104,1353,1356,1410,1425,1521,1596,1599,1620,1629,1674,1872,2064,2139,2352,2448,2487,2526,2553,2586,2655,2670,2685,2691,2703,2850,2994,3024,3138,3237,3243,3249

<223> n = A,T,C or G if after CG;

n = T or C if after AG

<221> misc_feature

<222> all "n" not specified above

<223> n = A,T,C or G

<400> 9

atg wsn tty gar ggn gcn mgn ytn wsn atg mgn wsn mgn mgn aay ggn	48
Met Ser Phe Glu Gly Ala Arg Leu Ser Met Arg Ser Arg Arg Asn Gly	
1 5 10 15	
acn atg ggn wsn acn mgn acn ytn tay wsn wsn gtn wsn mgn wsn acn	96
Thr Met Gly Ser Thr Arg Thr Leu Tyr Ser Ser Val Ser Arg Ser Thr	
20 25 30	
gay gtn wsn tay wsn gay wsn gay ytn gtn aay tty ath car gcn aay	144
Asp Val Ser Tyr Ser Asp Ser Asp Leu Val Asn Phe Ile Gln Ala Asn	
35 40 45	
tty aar aar mgn gar tgy gtn tty tty acn mgn gay wsn aar gcn atg	192
Phe Lys Lys Arg Glu Cys Val Phe Phe Thr Arg Asp Ser Lys Ala Met	
50 55 60	
gar aay ath tgy aar tgy ggn tay gcn car wsn car cay ath gar ggn	240
Glu Asn Ile Cys Lys Cys Gly Tyr Ala Gln Ser Gln His Ile Glu Gly	
65 70 75 80	
acn car ath aay car aay gar aar tgg aay tay aar aar cay acn aar	288
Thr Gln Ile Asn Gln Asn Glu Lys Trp Asn Tyr Lys Lys His Thr Lys	
85 90 95	
gar tty ccn acn gay gcn tty ggn gay ath car tty gar acn ytn ggn	336
Glu Phe Pro Thr Asp Ala Phe Gly Asp Ile Gln Phe Glu Thr Leu Gly	
100 105 110	
aar aar ggn aar tay ytn mgn ytn wsn tgy gay acn gay wsn gar acn	384
Lys Lys Gly Lys Tyr Leu Arg Leu Ser Cys Asp Thr Asp Ser Glu Thr	
115 120 125	
ytn tay gar ytn ytn acn car cay tgg cay ytn aar acn ccn aay ytn	432
Leu Tyr Glu Leu Leu Thr Gln His Trp His Leu Lys Thr Pro Asn Leu	
130 135 140	
gtn ath wsn gtn acn ggn ggn gcn aar aay tty gcn ytn aar ccn mgn	480
Val Ile Ser Val Thr Gly Gly Ala Lys Asn Phe Ala Leu Lys Pro Arg	
145 150 155 160	
atg mgn aar ath tty wsn mgn ytn ath tay ath gcn car wsn aar ggn	528
Met Arg Lys Ile Phe Ser Arg Leu Ile Tyr Ile Ala Gln Ser Lys Gly	
165 170 175	
gcn tgg ath ytn acn ggn ggn acn cay tay ggn ytn atg aar tay ath	576
Ala Trp Ile Leu Thr Gly Gly Thr His Tyr Gly Leu Met Lys Tyr Ile	
180 185 190	
ggn gar gtn gtn mgn gay aay acn ath wsn mgn aay wsn gar gar aay	624
Gly Glu Val Val Arg Asp Asn Thr Ile Ser Arg Asn Ser Glu Glu Asn	
195 200 205	
ath gtn gcn ath ggn ath gcn gcn tgg ggn atg gtn wsn aay mgn gay	672
Ile Val Ala Ile Gly Ile Ala Ala Trp Gly Met Val Ser Asn Arg Asp	
210 215 220	
acn ytn ath mgn wsn tgy gay gay gar ggn cay tty wsn gcn car tay	720
Thr Leu Ile Arg Ser Cys Asp Asp Glu Gly His Phe Ser Ala Gln Tyr	
225 230 235 240	
ath atg gay gay tty acn mgn gay ccn ytn tay ath ytn gay aay aay	768
Ile Met Asp Asp Phe Thr Arg Asp Pro Leu Tyr Ile Leu Asp Asn Asn	
245 250 255	
cay acn cay ytn ytn ytn gtn gay aay ggn tgy cay ggn cay ccn acn	816
His Thr His Leu Leu Leu Val Asp Asn Gly Cys His Gly His Pro Thr	

26/75

260					265					270						
gtn	gar	gcn	aar	ytn	mgn	aay	car	ytn	gar	aar	tay	ath	wsn	gar	mgn	864
Val	Glu	Ala	Lys	Leu	Arg	Asn	Gln	Leu	Glu	Lys	Tyr	Ile	Ser	Glu	Arg	
		275					280					285				
acn	wsn	car	gay	wsn	aay	tay	ggn	ggn	aar	ath	ccn	ath	gtn	tgy	tty	912
Thr	Ser	Gln	Asp	Ser	Asn	Tyr	Gly	Gly	Lys	Ile	Pro	Ile	Val	Cys	Phe	
	290					295					300					
gcn	car	ggn	ggn	ggn	mgn	gar	acn	ytn	aar	gcn	ath	aay	acn	wsn	gtn	960
Ala	Gln	Gly	Gly	Gly	Arg	Glu	Thr	Leu	Lys	Ala	Ile	Asn	Thr	Ser	Val	
305					310					315					320	
aar	wsn	aar	ath	ccn	tgy	gtn	gtn	gtn	gar	ggn	wsn	ggn	car	ath	gcn	1008
Lys	Ser	Lys	Ile	Pro	Cys	Val	Val	Val	Glu	Gly	Ser	Gly	Gln	Ile	Ala	
				325					330					335		
gay	gtn	ath	gcn	wsn	ytn	gtn	gar	gtn	gar	gay	gtn	ytn	acn	wsn	wsn	1056
Asp	Val	Ile	Ala	Ser	Leu	Val	Glu	Val	Glu	Asp	Val	Leu	Thr	Ser	Ser	
		340					345						350			
atg	gtn	aar	gar	aar	ytn	gtn	mgn	tty	ytn	ccn	mgn	acn	gtn	wsn	mgn	1104
Met	Val	Lys	Glu	Lys	Leu	Val	Arg	Phe	Leu	Pro	Arg	Thr	Val	Ser	Arg	
		355					360					365				
ytn	ccn	gar	gar	gar	ath	gar	wsn	tgg	ath	aar	tgg	ytn	aar	gar	ath	1152
Leu	Pro	Glu	Glu	Glu	Ile	Glu	Ser	Trp	Ile	Lys	Trp	Leu	Lys	Glu	Ile	
	370					375					380					
ytn	gar	wsn	wsn	cay	ytn	ytn	acn	gtn	ath	aar	atg	gar	gar	gcn	ggn	1200
Leu	Glu	Ser	Ser	His	Leu	Leu	Thr	Val	Ile	Lys	Met	Glu	Glu	Ala	Gly	
	385				390					395					400	
gay	gar	ath	gtn	wsn	aay	gcn	ath	wsn	tay	gcn	ytn	tay	aar	gcn	tty	1248
Asp	Glu	Ile	Val	Ser	Asn	Ala	Ile	Ser	Tyr	Ala	Leu	Tyr	Lys	Ala	Phe	
				405					410					415		
wsn	acn	aay	gar	car	gay	aar	gay	aay	tgg	aay	ggn	car	ytn	aar	ytn	1296
Ser	Thr	Asn	Glu	Gln	Asp	Lys	Asp	Asn	Trp	Asn	Gly	Gln	Leu	Lys	Leu	
			420					425					430			
ytn	ytn	gar	tgg	aay	car	ytn	gay	ytn	gcn	wsn	gay	gar	ath	tty	acn	1344
Leu	Leu	Glu	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Ser	Asp	Glu	Ile	Phe	Thr	
		435					440					445				
aay	gay	mgn	mgn	tgg	gar	wsn	gcn	gay	ytn	car	gar	gtn	atg	tty	acn	1392
Asn	Asp	Arg	Arg	Trp	Glu	Ser	Ala	Asp	Leu	Gln	Glu	Val	Met	Phe	Thr	
	450					455					460					
gcn	ytn	ath	aar	gay	mgn	ccn	aar	tty	gtn	mgn	ytn	tty	ytn	gar	aay	1440
Ala	Leu	Ile	Lys	Asp	Arg	Pro	Lys	Phe	Val	Arg	Leu	Phe	Leu	Glu	Asn	
465					470					475					480	
ggn	ytn	aay	ytn	car	aar	tty	ytn	acn	aay	gar	gtn	ytn	acn	gar	ytn	1488
Gly	Leu	Asn	Leu	Gln	Lys	Phe	Leu	Thr	Asn	Glu	Val	Leu	Thr	Glu	Leu	
			485						490					495		
tty	wsn	acn	cay	tty	wsn	acn	ytn	gtn	tay	mgn	aay	ytn	car	ath	gcn	1536
Phe	Ser	Thr	His	Phe	Ser	Thr	Leu	Val	Tyr	Arg	Asn	Leu	Gln	Ile	Ala	
			500					505					510			
aar	aay	wsn	tay	aay	gay	gcn	ytn	ytn	acn	tty	gtn	tgg	aar	ytn	gtn	1584
Lys	Asn	Ser	Tyr	Asn	Asp	Ala	Leu	Leu	Thr	Phe	Val	Trp	Lys	Leu	Val	
		515					520					525				
gcn	aay	tty	mgn	mgn	wsn	tty	tgg	aar	gar	gay	mgn	wsn	wsn	mgn	gar	1632
Ala	Asn	Phe	Arg	Arg	Ser	Phe	Trp	Lys	Glu	Asp	Arg	Ser	Ser	Arg	Glu	

530	535	540	
gay ytn gay gtn gar ytn cay gay gcn wsn ytn acn acn mgn cay ccn Asp Leu Asp Val Glu Leu His Asp Ala Ser Leu Thr Thr Arg His Pro 545 550 555 560			1680
ytn car gcn ytn tty ath tgg gcn ath ytn car aay aar aar gar ytn Leu Gln Ala Leu Phe Ile Trp Ala Ile Leu Gln Asn Lys Lys Glu Leu 565 570 575			1728
wsn aar gtn ath tgg gar car acn aar ggn tgy acn ytn gcn gcn ytn Ser Lys Val Ile Trp Glu Gln Thr Lys Gly Cys Thr Leu Ala Ala Leu 580 585 590			1776
ggn gcn wsn aar ytn ytn aar acn ytn gcn aar gtn aar aay gay ath Gly Ala Ser Lys Leu Leu Lys Thr Leu Ala Lys Val Lys Asn Asp Ile 595 600 605			1824
aay gcn gcn ggn gar wsn gar gar ytn gcn aay gar tay gar acn mgn Asn Ala Ala Gly Glu Ser Glu Glu Leu Ala Asn Glu Tyr Glu Thr Arg 610 615 620			1872
gcn gtn gar ytn tty acn gar tgy tay wsn aay gay gar gay ytn gcn Ala Val Glu Leu Phe Thr Glu Cys Tyr Ser Asn Asp Glu Asp Leu Ala 625 630 635 640			1920
gar car ytn ytn gtn tay wsn tgy gar gcn tgg ggn ggn wsn aay tgy Glu Gln Leu Leu Val Tyr Ser Cys Glu Ala Trp Gly Gly Ser Asn Cys 645 650 655			1968
ytn gar ytn gcn gtn gar gcn acn gay car cay tty ath gcn car ccn Leu Glu Leu Ala Val Glu Ala Thr Asp Gln His Phe Ile Ala Gln Pro 660 665 670			2016
ggn gtn car aay tty ytn wsn aar car tgg tay ggn gar ath wsn mgn Gly Val Gln Asn Phe Leu Ser Lys Gln Trp Tyr Gly Glu Ile Ser Arg 675 680 685			2064
gay acn aar aay tgg aar ath ath ytn tgy ytn tty ath ath ccn ytn Asp Thr Lys Asn Trp Lys Ile Ile Leu Cys Leu Phe Ile Ile Pro Leu 690 695 700			2112
gtn ggn tgy ggn ytn gtn wsn tty mgn aar aar ccn ath gay aar cay Val Gly Cys Gly Leu Val Ser Phe Arg Lys Lys Pro Ile Asp Lys His 705 710 715 720			2160
aar aar ytn ytn tgg tay tay gtn gcn tty tty acn wsn ccn tty gtn Lys Lys Leu Leu Trp Tyr Tyr Val Ala Phe Phe Thr Ser Pro Phe Val 725 730 735			2208
gtn tty wsn tgg aay gtn gtn tty tay ath gcn tty ytn ytn ytn tty Val Phe Ser Trp Asn Val Val Phe Tyr Ile Ala Phe Leu Leu Leu Phe 740 745 750			2256
gcn tay gtn ytn ytn atg gay tty cay wsn gtn ccn cay acn ccn gar Ala Tyr Val Leu Leu Met Asp Phe His Ser Val Pro His Thr Pro Glu 755 760 765			2304
ytn ath ytn tay gcn ytn gtn tty gtn ytn tty tgy gay gar gtn mgn Leu Ile Leu Tyr Ala Leu Val Phe Val Leu Phe Cys Asp Glu Val Arg 770 775 780			2352
car tgg tay atg aay ggn gtn aay tay tty acn gay ytn tgg aay gtn Gln Trp Tyr Met Asn Gly Val Asn Tyr Phe Thr Asp Leu Trp Asn Val 785 790 795 800			2400
atg gay acn ytn ggn ytn tty tay tty ath gcn ggn ath gtn tty mgn Met Asp Thr Leu Gly Leu Phe Tyr Phe Ile Ala Gly Ile Val Phe Arg			2448

28/75

805								810					815					
ytn	cay	wsn	wsn	aay	aar	wsn	wsn	ytn	tay	wsn	ggn	mgn	gtn	ath	tty	2496		
Leu	His	Ser	Ser	Asn	Lys	Ser	Ser	Leu	Tyr	Ser	Gly	Arg	Val	Ile	Phe			
			820					825					830					
tgy	ytn	gay	tay	ath	ath	tty	acn	ytn	mgn	ytn	ath	cay	ath	tty	acn	2544		
Cys	Leu	Asp	Tyr	Ile	Ile	Phe	Thr	Leu	Arg	Leu	Ile	His	Ile	Phe	Thr			
		835					840					845						
gtn	wsn	mgn	aay	ytn	ggn	ccn	aar	ath	ath	atg	ytn	car	mgn	atg	ytn	2592		
Val	Ser	Arg	Asn	Leu	Gly	Pro	Lys	Ile	Ile	Met	Leu	Gln	Arg	Met	Leu			
	850					855					860							
ath	gay	gtn	tty	tty	tty	ytn	tty	ytn	tty	gcn	gtn	tgg	atg	gtn	gcn	2640		
Ile	Asp	Val	Phe	Phe	Phe	Leu	Phe	Leu	Phe	Ala	Val	Trp	Met	Val	Ala			
865					870					875					880			
tty	ggn	gtn	gcn	mgn	car	ggn	ath	ytn	mgn	car	aay	gar	car	mgn	tgg	2688		
Phe	Gly	Val	Ala	Arg	Gln	Gly	Ile	Leu	Arg	Gln	Asn	Glu	Gln	Arg	Trp			
				885					890					895				
mgn	tgg	ath	tty	mgn	wsn	gtn	ath	tay	gar	ccn	tay	ytn	gcn	atg	tty	2736		
Arg	Trp	Ile	Phe	Arg	Ser	Val	Ile	Tyr	Glu	Pro	Tyr	Leu	Ala	Met	Phe			
			900					905					910					
ggn	car	gtn	ccn	wsn	gay	gtn	gay	wsn	acn	acn	tay	gay	tty	wsn	cay	2784		
Gly	Gln	Val	Pro	Ser	Asp	Val	Asp	Ser	Thr	Thr	Tyr	Asp	Phe	Ser	His			
		915					920					925						
tgy	acn	tty	wsn	ggn	aay	gar	wsn	aar	ccn	ytn	tgy	gtn	gar	ytn	gay	2832		
Cys	Thr	Phe	Ser	Gly	Asn	Glu	Ser	Lys	Pro	Leu	Cys	Val	Glu	Leu	Asp			
	930					935					940							
gar	cay	aay	ytn	ccn	mgn	tty	ccn	gar	tgg	ath	acn	ath	ccn	ytn	gtn	2880		
Glu	His	Asn	Leu	Pro	Arg	Phe	Pro	Glu	Trp	Ile	Thr	Ile	Pro	Leu	Val			
945					950					955					960			
tgy	ath	tay	atg	ytn	wsn	acn	aay	ath	ytn	ytn	gtn	aay	ytn	ytn	gtn	2928		
Cys	Ile	Tyr	Met	Leu	Ser	Thr	Asn	Ile	Leu	Leu	Val	Asn	Leu	Leu	Val			
				965					970					975				
gcn	atg	tty	ggn	tay	acn	gtn	ggn	ath	gtn	car	gar	aay	aay	gay	car	2976		
Ala	Met	Phe	Gly	Tyr	Thr	Val	Gly	Ile	Val	Gln	Glu	Asn	Asn	Asp	Gln			
			980					985					990					
gtn	tgg	aar	tty	car	mgn	tay	tty	ytn	gtn	car	gar	tay	tgy	aay	mgn	3024		
Val	Trp	Lys	Phe	Gln	Arg	Tyr	Phe	Leu	Val	Gln	Glu	Tyr	Cys	Asn	Arg			
		995					1000					1005						
ytn	aay	ath	ccn	tty	ccn	tty	gtn	gtn	tty	gcn	tay	tty	tay	atg	gtn	3072		
Leu	Asn	Ile	Pro	Phe	Pro	Phe	Val	Val	Phe	Ala	Tyr	Phe	Tyr	Met	Val			
	1010					1015					1020							
gtn	aar	aar	tgy	tty	aar	tgy	tgy	tgy	aar	gar	aar	aay	atg	gar	wsn	3120		
Val	Lys	Lys	Cys	Phe	Lys	Cys	Cys	Cys	Lys	Glu	Lys	Asn	Met	Glu	Ser			
	1025				1030					1035					1040			
aay	gcn	tgy	tgy	tty	mgn	aay	gar	gay	aay	gar	acn	ytn	gcn	tgg	gar	3168		
Asn	Ala	Cys	Cys	Phe	Arg	Asn	Glu	Asp	Asn	Glu	Thr	Leu	Ala	Trp	Glu			
				1045					1050					1055				
ggn	gtn	atg	aar	gar	aay	tay	ytn	gtn	aar	ath	aay	acn	aar	gcn	aay	3216		
Gly	Val	Met	Lys	Glu	Asn	Tyr	Leu	Val	Lys	Ile	Asn	Thr	Lys	Ala	Asn			
			1060					1065					1070					
gay	aay	wsn	gar	gar	atg	mgn	cay	mgn	tty	mgn	car	ytn	gay	wsn	aar	3264		
Asp	Asn	Ser	Glu	Glu	Met	Arg	His	Arg	Phe	Arg	Gln	Leu	Asp	Ser	Lys			

29/75

1075	1080	1085	
ytn aay gay ytn aar wsn ytn ytn aar gar ath gcn aay aay ath aar			3312
Leu Asn Asp Leu Lys Ser	Leu Leu Lys Glu Ile	Ala Asn Asn Ile Lys	
1090	1095	1100	
<210> 10			
<211> 3867			
<212> DNA			
<213> Homo sapiens			
<220>			
<221> CDS			
<222> (61) ... (3867)			
<400> 10			
cagaaggaag atggagcagt tctgctaacc cgagtgggtcc tggaatgtgt ttttcttccc			60
atg ccg tta cca cat aaa agt ggt cag aaa tca ctc aga tct tat ttt			108
Met Pro Leu Pro His Lys Ser Gly Gln Lys Ser Leu Arg Ser Tyr Phe			
1 5 10 15			
gtc ttc tca atc caa gtt tgc gta att cag ata aaa ggc aca gaa agc			156
Val Phe Ser Ile Gln Val Ser Val Ile Gln Ile Lys Gly Thr Glu Ser			
20 25 30			
cct ggg ttt gcc tgg tgg gca ttc tct gga cca ctc ttc cgg ttc ttg			204
Pro Gly Phe Ala Trp Trp Ala Phe Ser Gly Pro Leu Phe Arg Phe Leu			
35 40 45			
cct ttc tcc gtg ttg ctg gcc ttg gag ctg acc gtg gtg ctg aca gga			252
Pro Phe Ser Val Leu Leu Ala Leu Glu Leu Thr Val Val Leu Thr Gly			
50 55 60			
gtc tgg cgc ctc ctg cgc cct tgc tat cat tgt gtg tac tgt gga ccc			300
Val Trp Arg Leu Leu Arg Pro Cys Tyr His Cys Val Tyr Cys Gly Pro			
65 70 75 80			
gca gca tgc gct cac ctg ttt ata aaa cag tgg ctg gat ggt tgg agg			348
Ala Ala Ser Ala His Leu Phe Ile Lys Gln Trp Leu Asp Gly Trp Arg			
85 90 95			
atg cag gtg gac aga aga cgt gga gcc tgc aga agt aaa ggc ttg gtg			396
Met Gln Val Asp Arg Arg Arg Gly Ala Cys Arg Ser Lys Gly Leu Val			
100 105 110			
cag gtt gaa ggg gct aca cag gca ggt gag cac ttg ctc agc ctg ggc			444
Gln Val Glu Gly Ala Thr Gln Ala Gly Glu His Leu Leu Ser Leu Gly			
115 120 125			
att gtg ggg cat ctc cct gaa gaa atg atg agt gag ctg agc ctg gag			492
Ile Val Gly His Leu Pro Glu Glu Met Met Ser Glu Leu Ser Leu Glu			
130 135 140			
gat gag cag gag atg aca gct gga ggg gta tgg gga aga ggg ctc tgg			540
Asp Glu Gln Glu Met Thr Ala Gly Gly Val Trp Gly Arg Gly Leu Trp			
145 150 155 160			
aca gaa gaa aag atg tcc ttt cgg gca gcc agg ctc agc atg agg aac			588
Thr Glu Glu Lys Met Ser Phe Arg Ala Ala Arg Leu Ser Met Arg Asn			
165 170 175			
aga agg aat gac act ctg gac agc acc cgg acc ctg tac tcc agc gcg			636
Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr Ser Ser Ala			
180 185 190			
tct cgg agc aca gac ttg tct tac agt gaa agc gac ttg gtg aat ttt			684

30/75

Ser	Arg	Ser	Thr	Asp	Leu	Ser	Tyr	Ser	Glu	Ser	Asp	Leu	Val	Asn	Phe	
		195					200					205				
att	caa	gca	aat	ttt	aag	aaa	cga	gaa	tgt	gtc	ttc	ttt	atc	aaa	gat	732
Ile	Gln	Ala	Asn	Phe	Lys	Lys	Arg	Glu	Cys	Val	Phe	Phe	Ile	Lys	Asp	
	210					215					220					
tcc	aag	gcc	acg	gag	aat	gtg	tgc	aag	tgt	ggc	tat	gcc	cag	agc	cag	780
Ser	Lys	Ala	Thr	Glu	Asn	Val	Cys	Lys	Cys	Gly	Tyr	Ala	Gln	Ser	Gln	
	225				230					235					240	
cac	atg	gaa	ggc	acc	cag	atc	aac	caa	agt	gag	aaa	tgg	aac	tac	aag	828
His	Met	Glu	Gly	Thr	Gln	Ile	Asn	Gln	Ser	Glu	Lys	Trp	Asn	Tyr	Lys	
				245					250					255		
aaa	cac	acc	aag	gaa	ttt	cct	acc	gac	gcc	ttt	ggg	gat	att	cag	ttt	876
Lys	His	Thr	Lys	Glu	Phe	Pro	Thr	Asp	Ala	Phe	Gly	Asp	Ile	Gln	Phe	
			260					265					270			
gag	aca	ctg	ggg	aag	aaa	ggg	aag	tat	ata	cgt	ctg	tcc	tgc	gac	acg	924
Glu	Thr	Leu	Gly	Lys	Lys	Gly	Lys	Tyr	Ile	Arg	Leu	Ser	Cys	Asp	Thr	
		275					280					285				
gac	gcg	gaa	atc	ctt	tac	gag	ctg	ctg	acc	cag	cac	tgg	cac	ctg	aaa	972
Asp	Ala	Glu	Ile	Leu	Tyr	Glu	Leu	Leu	Thr	Gln	His	Trp	His	Leu	Lys	
	290					295					300					
aca	ccc	aac	ctg	gtc	att	tct	gtg	acc	ggg	ggc	gcc	aag	aac	ttc	gcc	1020
Thr	Pro	Asn	Leu	Val	Ile	Ser	Val	Thr	Gly	Gly	Ala	Lys	Asn	Phe	Ala	
	305				310					315					320	
ctg	aag	ccg	cgc	atg	cgc	aag	atc	ttc	agc	cgg	ctc	atc	tac	atc	gcg	1068
Leu	Lys	Pro	Arg	Met	Arg	Lys	Ile	Phe	Ser	Arg	Leu	Ile	Tyr	Ile	Ala	
				325					330					335		
cag	tcc	aaa	ggt	gct	tgg	att	ctc	acg	gga	ggc	acc	cat	tat	ggc	ctg	1116
Gln	Ser	Lys	Gly	Ala	Trp	Ile	Leu	Thr	Gly	Gly	Thr	His	Tyr	Gly	Leu	
			340					345					350			
atg	aag	tac	atc	ggg	gag	gtg	gtg	aga	gat	aac	acc	atc	agc	agg	agt	1164
Met	Lys	Tyr	Ile	Gly	Glu	Val	Val	Arg	Asp	Asn	Thr	Ile	Ser	Arg	Ser	
		355					360					365				
tca	gag	gag	aat	att	gtg	gcc	att	ggc	ata	gca	gct	tgg	ggc	atg	gtc	1212
Ser	Glu	Glu	Asn	Ile	Val	Ala	Ile	Gly	Ile	Ala	Ala	Trp	Gly	Met	Val	
	370					375					380					
tcc	aac	cgg	gac	acc	ctc	atc	agg	aat	tgc	gat	gct	gag	ggc	tat	ttt	1260
Ser	Asn	Arg	Asp	Thr	Leu	Ile	Arg	Asn	Cys	Asp	Ala	Glu	Gly	Tyr	Phe	
	385				390					395					400	
tta	gcc	cag	tac	ctt	atg	gat	gac	ttc	aca	aga	gat	cca	ctg	tat	atc	1308
Leu	Ala	Gln	Tyr	Leu	Met	Asp	Asp	Phe	Thr	Arg	Asp	Pro	Leu	Tyr	Ile	
				405					410					415		
ctg	gac	aac	aac	cac	aca	cat	ttg	ctg	ctc	gtg	gac	aat	ggc	tgt	cat	1356
Leu	Asp	Asn	Asn	His	Thr	His	Leu	Leu	Leu	Val	Asp	Asn	Gly	Cys	His	
				420				425					430			
gga	cat	ccc	act	gtc	gaa	gca	aag	ctc	cgg	aat	cag	cta	gag	aag	tat	1404
Gly	His	Pro	Thr	Val	Glu	Ala	Lys	Leu	Arg	Asn	Gln	Leu	Glu	Lys	Tyr	
		435					440					445				
atc	tct	gag	cgc	act	att	caa	gat	tcc	aac	tat	ggg	ggc	aag	atc	ccc	1452
Ile	Ser	Glu	Arg	Thr	Ile	Gln	Asp	Ser	Asn	Tyr	Gly	Gly	Lys	Ile	Pro	
	450					455					460					
att	gtg	tgt	ttt	gcc	caa	gga	ggg	gga	aaa	gag	act	ttg	aaa	gcc	atc	1500

31/75

Ile 465	Val	Cys	Phe	Ala	Gln 470	Gly	Gly	Gly	Lys	Glu 475	Thr	Leu	Lys	Ala	Ile 480	
aat Asn	acc Thr	tcc Ser	atc Ile	aaa Lys 485	aat Asn	aaa Lys	att Ile	cct Pro	tgt Cys 490	gtg Val	gtg Val	gtg Val	gaa Glu	ggc Gly 495	tgc Ser	1548
ggc Gly	cag Gln	atc Ile	gct Ala 500	gat Asp	gtg Val	atc Ile	gct Ala	agc Ser 505	ctg Leu	gtg Val	gag Glu	gtg Val	gag Glu 510	gat Asp	gcc Ala	1596
ctg Leu	aca Thr	tct Ser 515	tct Ser	gcc Ala	gtc Val	aag Lys	gag Glu 520	aag Lys	ctg Leu	gtg Val	cgc Arg	ttt Phe 525	tta Leu	ccc Pro	cgc Arg	1644
acg Thr	gtg Val 530	tcc Ser	cgg Arg	ctg Leu	cct Pro	gag Glu 535	gag Glu	gag Glu	act Thr	gag Glu	agt Ser 540	tgg Trp	atc Ile	aaa Lys	tgg Trp	1692
ctc Leu 545	aaa Lys	gaa Glu	att Ile	ctc Leu	gaa Glu 550	tgt Cys	tct Ser	cac His	cta Leu	tta Leu 555	aca Thr	gtt Val	att Ile	aaa Lys	atg Met 560	1740
gaa Glu	gaa Glu	gct Ala	ggg Gly	gat Asp 565	gaa Glu	att Ile	gtg Val	agc Ser	aat Asn 570	gcc Ala	atc Ile	tcc Ser	tac Tyr	gct Ala 575	cta Leu	1788
tac Tyr	aaa Lys	gcc Ala	ttc Phe 580	agc Ser	acc Thr	agt Ser	gag Glu	caa Gln 585	gac Asp	aag Lys	gat Asp	aac Asn	tgg Trp 590	aat Asn	ggg Gly	1836
cag Gln	ctg Leu	aag Lys 595	ctt Leu	ctg Leu	ctg Leu	gag Glu	tgg Trp 600	aac Asn	cag Gln	ctg Leu	gac Asp	tta Leu 605	gcc Ala	aat Asn	gat Asp	1884
gag Glu 610	att Ile	ttc Phe	acc Thr	aat Asn	gac Asp 615	cgc Arg	cga Arg	tgg Trp	gag Glu	tct Ser	gct Ala 620	gac Asp	ctt Leu	caa Gln	gaa Glu	1932
gtc Val 625	atg Met	ttt Phe	acg Thr	gct Ala	ctc Leu 630	ata Ile	aag Lys	gac Asp	aga Arg	ccc Pro 635	aag Lys	ttt Phe	gtc Val	cgc Arg	ctc Leu 640	1980
ttt Phe	ctg Leu	gag Glu	aat Asn	ggc Gly 645	ttg Leu	aac Asn	cta Leu	cgg Arg	aag Lys 650	ttt Phe	ctc Leu	acc Thr	cat His	gat Asp 655	gtc Val	2028
ctc Leu	act Thr	gaa Glu 660	ctc Leu	ttc Phe	tcc Ser	aac Asn	cac His	ttc Phe 665	agc Ser	acg Thr	ctt Leu	gtg Val	tac Tyr 670	cgg Arg	aat Asn	2076
ctg Leu	cag Gln	atc Ile 675	gcc Ala	aag Lys	aat Asn	tcc Ser	tat Tyr 680	aat Asn	gat Asp	gcc Ala	ctc Leu	ctc Leu 685	acg Thr	ttt Phe	gtc Val	2124
tgg Trp 690	aaa Lys	ctg Leu	gtt Val	gcg Ala	aac Asn	ttc Phe 695	cga Arg	aga Arg	ggc Gly	ttc Phe 700	cgg Arg	aag Lys	gaa Glu	gac Asp	aga Arg	2172
aat Asn 705	ggc Gly	cgg Arg	gac Asp	gag Glu	atg Met 710	gac Asp	ata Ile	gaa Glu	ctc Leu	cac His 715	gac Asp	gtg Val	tct Ser	cct Pro	att Ile 720	2220
act Thr	cgg Arg	cac His	ccc Pro	ctg Leu 725	caa Gln	gct Ala	ctc Leu	ttc Phe	atc Ile 730	tgg Trp	gcc Ala	att Ile	ctt Leu	cag Gln 735	aat Asn	2268
aag	aag	gaa	ctc	tcc	aaa	gtc	att	tgg	gag	cag	acc	agg	ggc	tgc	act	2316

32/75

Lys	Lys	Glu	Leu	Ser	Lys	Val	Ile	Trp	Glu	Gln	Thr	Arg	Gly	Cys	Thr	
			740					745					750			
ctg	gca	gcc	ctg	gga	gcc	agc	aag	ctt	ctg	aag	act	ctg	gcc	aaa	gtg	2364
Leu	Ala	Ala	Leu	Gly	Ala	Ser	Lys	Leu	Leu	Lys	Thr	Leu	Ala	Lys	Val	
		755					760					765				
aag	aac	gac	atc	aat	gct	gct	ggg	gag	tcc	gag	gag	ctg	gct	aat	gag	2412
Lys	Asn	Asp	Ile	Asn	Ala	Ala	Gly	Glu	Ser	Glu	Glu	Leu	Ala	Asn	Glu	
	770					775					780					
tac	gag	acc	cgg	gct	gtt	gag	ctg	ttc	act	gag	tgt	tac	agc	agc	gat	2460
Tyr	Glu	Thr	Arg	Ala	Val	Glu	Leu	Phe	Thr	Glu	Cys	Tyr	Ser	Ser	Asp	
785					790					795					800	
gaa	gac	ttg	gca	gaa	cag	ctg	ctg	gtc	tat	tcc	tgt	gaa	gct	tgg	ggt	2508
Glu	Asp	Leu	Ala	Glu	Gln	Leu	Leu	Val	Tyr	Ser	Cys	Glu	Ala	Trp	Gly	
				805					810					815		
gga	agc	aac	tgt	ctg	gag	ctg	gcg	gtg	gag	gcc	aca	gac	cag	cat	ttc	2556
Gly	Ser	Asn	Cys	Leu	Glu	Leu	Ala	Val	Glu	Ala	Thr	Asp	Gln	His	Phe	
			820					825					830			
atc	gcc	cag	cct	ggg	gtc	cag	aat	ttt	ctt	tct	aag	caa	tgg	tat	gga	2604
Ile	Ala	Gln	Pro	Gly	Val	Gln	Asn	Phe	Leu	Ser	Lys	Gln	Trp	Tyr	Gly	
		835					840					845				
gag	att	tcc	cga	gac	acc	aag	aac	tgg	aag	att	atc	ctg	tgt	ctg	ttt	2652
Glu	Ile	Ser	Arg	Asp	Thr	Lys	Asn	Trp	Lys	Ile	Ile	Leu	Cys	Leu	Phe	
	850					855					860					
att	ata	ccc	ttg	gtg	ggc	tgt	ggc	ttt	gta	tca	ttt	agg	aag	aaa	cct	2700
Ile	Ile	Pro	Leu	Val	Gly	Cys	Gly	Phe	Val	Ser	Phe	Arg	Lys	Lys	Pro	
865					870					875					880	
gtc	gac	aag	cac	aag	aag	ctg	ctt	tgg	tac	tat	gtg	gcg	ttc	ttc	acc	2748
Val	Asp	Lys	His	Lys	Lys	Leu	Leu	Trp	Tyr	Tyr	Val	Ala	Phe	Phe	Thr	
				885					890					895		
tcc	ccc	ttc	gtg	gtc	ttc	tcc	tgg	aat	gtg	gtc	ttc	tac	atc	gcc	ttc	2796
Ser	Pro	Phe	Val	Val	Phe	Ser	Trp	Asn	Val	Val	Phe	Tyr	Ile	Ala	Phe	
			900					905					910			
ctc	ctg	ctg	ttt	gcc	tac	gtg	ctg	ctc	atg	gat	ttc	cat	tcg	gtg	cca	2844
Leu	Leu	Leu	Phe	Ala	Tyr	Val	Leu	Leu	Met	Asp	Phe	His	Ser	Val	Pro	
		915					920					925				
cac	ccc	ccc	gag	ctg	gtc	ctg	tac	tcg	ctg	gtc	ttt	gtc	ctc	ttc	tgt	2892
His	Pro	Pro	Glu	Leu	Val	Leu	Tyr	Ser	Leu	Val	Phe	Val	Leu	Phe	Cys	
	930					935					940					
gat	gaa	gtg	aga	cag	tgg	tac	gta	aat	ggg	gtg	aat	tat	ttt	act	gac	2940
Asp	Glu	Val	Arg	Gln	Trp	Tyr	Val	Asn	Gly	Val	Asn	Tyr	Phe	Thr	Asp	
945					950				955					960		
ctg	tgg	aat	gtg	atg	gac	acg	ctg	ggg	ctt	ttt	tac	ttc	ata	gca	gga	2988
Leu	Trp	Asn	Val	Met	Asp	Thr	Leu	Gly	Leu	Phe	Tyr	Phe	Ile	Ala	Gly	
				965					970					975		
att	gta	ttt	cgg	ctc	cac	tct	tct	aat	aaa	agc	tct	ttg	tat	tct	gga	3036
Ile	Val	Phe	Arg	Leu	His	Ser	Ser	Asn	Lys	Ser	Ser	Leu	Tyr	Ser	Gly	
			980					985					990			
cga	gtc	att	ttc	tgt	ctg	gac	tac	att	att	ttc	act	cta	aga	ttg	atc	3084
Arg	Val	Ile	Phe	Cys	Leu	Asp	Tyr	Ile	Ile	Phe	Thr	Leu	Arg	Leu	Ile	
		995					1000					1005				
cac	att	ttt	act	gta	agc	aga	aac	tta	gga	ccc	aag	att	ata	atg	ctg	3132

His	Ile	Phe	Thr	Val	Ser	Arg	Asn	Leu	Gly	Pro	Lys	Ile	Ile	Met	Leu		
1010						1015					1020						
cag	agg	atg	ctg	atc	gat	gtg	ttc	ttc	ttc	ctg	ttc	ctc	ttt	gcg	gtg	3180	
Gln	Arg	Met	Leu	Ile	Asp	Val	Phe	Phe	Phe	Leu	Phe	Leu	Phe	Ala	Val		
1025					1030					1035					1040		
tgg	atg	gtg	gcc	ttt	ggc	gtg	gcc	agg	caa	ggg	atc	ctt	agg	cag	aat	3228	
Trp	Met	Val	Ala	Phe	Gly	Val	Ala	Arg	Gln	Gly	Ile	Leu	Arg	Gln	Asn		
				1045					1050					1055			
gag	cag	cgc	tgg	agg	tgg	ata	ttc	cgt	tgc	gtc	atc	tac	gag	ccc	tac	3276	
Glu	Gln	Arg	Trp	Arg	Trp	Ile	Phe	Arg	Ser	Val	Ile	Tyr	Glu	Pro	Tyr		
			1060					1065					1070				
ctg	gcc	atg	ttc	ggc	cag	gtg	ccc	agt	gac	gtg	gat	ggg	acc	acg	tat	3324	
Leu	Ala	Met	Phe	Gly	Gln	Val	Pro	Ser	Asp	Val	Asp	Gly	Thr	Thr	Tyr		
		1075					1080					1085					
gac	ttt	gcc	cac	tgc	acc	ttc	act	ggg	aat	gag	tcc	aag	cca	ctg	tgt	3372	
Asp	Phe	Ala	His	Cys	Thr	Phe	Thr	Gly	Asn	Glu	Ser	Lys	Pro	Leu	Cys		
	1090					1095				1100							
gtg	gag	ctg	gat	gag	cac	aac	ctg	ccc	cgg	ttc	ccc	gag	tgg	atc	acc	3420	
Val	Glu	Leu	Asp	Glu	His	Asn	Leu	Pro	Arg	Phe	Pro	Glu	Trp	Ile	Thr		
	1105				1110					1115					1120		
atc	ccc	ctg	gtg	tgc	atc	tac	atg	tta	tcc	acc	aac	atc	ctg	ctg	gtc	3468	
Ile	Pro	Leu	Val	Cys	Ile	Tyr	Met	Leu	Ser	Thr	Asn	Ile	Leu	Leu	Val		
				1125				1130						1135			
aac	ctg	ctg	gtc	gcc	atg	ttt	ggc	tac	acg	gtg	ggc	acc	gtc	cag	gag	3516	
Asn	Leu	Leu	Val	Ala	Met	Phe	Gly	Tyr	Thr	Val	Gly	Thr	Val	Gln	Glu		
			1140				1145						1150				
aac	aat	gac	cag	gtc	tgg	aag	ttc	cag	agg	tac	ttc	ctg	gtg	cag	gag	3564	
Asn	Asn	Asp	Gln	Val	Trp	Lys	Phe	Gln	Arg	Tyr	Phe	Leu	Val	Gln	Glu		
		1155				1160						1165					
tac	tgc	agc	cgc	ctc	aat	atc	ccc	ttc	ccc	ttc	atc	gtc	ttc	gct	tac	3612	
Tyr	Cys	Ser	Arg	Leu	Asn	Ile	Pro	Phe	Pro	Phe	Ile	Val	Phe	Ala	Tyr		
	1170				1175					1180							
ttc	tac	atg	gtg	gtg	aag	aag	tgc	ttc	aag	tgt	tgc	tgc	aag	gag	aaa	3660	
Phe	Tyr	Met	Val	Val	Lys	Lys	Cys	Phe	Lys	Cys	Cys	Cys	Lys	Glu	Lys		
	1185				1190					1195					1200		
aac	atg	gag	tct	tct	gtc	tgc	tgt	ttc	aaa	aat	gaa	gac	aat	gag	act	3708	
Asn	Met	Glu	Ser	Ser	Val	Cys	Cys	Phe	Lys	Asn	Glu	Asp	Asn	Glu	Thr		
				1205					1210					1215			
ctg	gca	tgg	gag	ggg	gtc	atg	aag	gaa	aac	tac	ctt	gtc	aag	atc	aac	3756	
Leu	Ala	Trp	Glu	Gly	Val	Met	Lys	Glu	Asn	Tyr	Leu	Val	Lys	Ile	Asn		
			1220					1225					1230				
aca	aaa	gcc	aac	gac	acc	tca	gag	gaa	atg	agg	cat	cga	ttt	aga	caa	3804	
Thr	Lys	Ala	Asn	Asp	Thr	Ser	Glu	Glu	Met	Arg	His	Arg	Phe	Arg	Gln		
		1235					1240					1245					
ctg	gat	aca	aag	ctt	aat	gat	ctc	aag	ggg	ctt	ctg	aaa	gag	att	gct	3852	
Leu	Asp	Thr	Lys	Leu	Asn	Asp	Leu	Lys	Gly	Leu	Leu	Lys	Glu	Ile	Ala		
	1250				1255					1260							
aat	aaa	atc	aaa	taa												3867	
Asn	Lys	Ile	Lys	*													
	1265																

<210> 11
 <211> 1268
 <212> PRT
 <213> Homo sapiens

<400> 11

```

Met Pro Leu Pro His Lys Ser Gly Gln Lys Ser Leu Arg Ser Tyr Phe
 1          5          10          15
Val Phe Ser Ile Gln Val Ser Val Ile Gln Ile Lys Gly Thr Glu Ser
          20          25          30
Pro Gly Phe Ala Trp Trp Ala Phe Ser Gly Pro Leu Phe Arg Phe Leu
          35          40          45
Pro Phe Ser Val Leu Leu Ala Leu Glu Leu Thr Val Val Leu Thr Gly
          50          55          60
Val Trp Arg Leu Leu Arg Pro Cys Tyr His Cys Val Tyr Cys Gly Pro
          65          70          75          80
Ala Ala Ser Ala His Leu Phe Ile Lys Gln Trp Leu Asp Gly Trp Arg
          85          90          95
Met Gln Val Asp Arg Arg Arg Gly Ala Cys Arg Ser Lys Gly Leu Val
          100          105          110
Gln Val Glu Gly Ala Thr Gln Ala Gly Glu His Leu Leu Ser Leu Gly
          115          120          125
Ile Val Gly His Leu Pro Glu Met Met Ser Glu Leu Ser Leu Glu
          130          135          140
Asp Glu Gln Glu Met Thr Ala Gly Gly Val Trp Gly Arg Gly Leu Trp
          145          150          155          160
Thr Glu Glu Lys Met Ser Phe Arg Ala Ala Arg Leu Ser Met Arg Asn
          165          170          175
Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr Ser Ser Ala
          180          185          190
Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu Val Asn Phe
          195          200          205
Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe Ile Lys Asp
          210          215          220
Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala Gln Ser Gln
          225          230          235          240
His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp Asn Tyr Lys
          245          250          255
Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp Ile Gln Phe
          260          265          270
Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser Cys Asp Thr
          275          280          285
Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp His Leu Lys
          290          295          300
Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys Asn Phe Ala
          305          310          315          320
Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile Tyr Ile Ala
          325          330          335
Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His Tyr Gly Leu
          340          345          350
Met Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile Ser Arg Ser
          355          360          365
Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp Gly Met Val
          370          375          380
Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu Gly Tyr Phe
          385          390          395          400
Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro Leu Tyr Ile
          405          410          415
Leu Asp Asn Asn His Thr His Leu Leu Val Asp Asn Gly Cys His
          420          425          430
Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu Glu Lys Tyr
          435          440          445
Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly Lys Ile Pro
          450          455          460
Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu Lys Ala Ile
          465          470          475          480
Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val Glu Gly Ser
          485          490          495

```


Gly	Gln	Ile	Ala	Asp	Val	Ile	Ala	Ser	Leu	Val	Glu	Val	Glu	Asp	Ala
			500					505					510		
Leu	Thr	Ser	Ser	Ala	Val	Lys	Glu	Lys	Leu	Val	Arg	Phe	Leu	Pro	Arg
		515					520					525			
Thr	Val	Ser	Arg	Leu	Pro	Glu	Glu	Thr	Glu	Ser	Thr	Ile	Lys	Trp	
		530				535					540				
Leu	Lys	Glu	Ile	Leu	Glu	Cys	Ser	His	Leu	Leu	Thr	Val	Ile	Lys	Met
545					550					555					560
Glu	Glu	Ala	Gly	Asp	Glu	Ile	Val	Ser	Asn	Ala	Ile	Ser	Tyr	Ala	Leu
			565						570					575	
Tyr	Lys	Ala	Phe	Ser	Thr	Ser	Glu	Gln	Asp	Lys	Asp	Asn	Trp	Asn	Gly
			580					585					590		
Gln	Leu	Lys	Leu	Leu	Leu	Glu	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Asn	Asp
		595					600					605			
Glu	Ile	Phe	Thr	Asn	Asp	Arg	Arg	Trp	Glu	Ser	Ala	Asp	Leu	Gln	Glu
	610					615					620				
Val	Met	Phe	Thr	Ala	Leu	Ile	Lys	Asp	Arg	Pro	Lys	Phe	Val	Arg	Leu
625					630					635					640
Phe	Leu	Glu	Asn	Gly	Leu	Asn	Leu	Arg	Lys	Phe	Leu	Thr	His	Asp	Val
			645						650					655	
Leu	Thr	Glu	Leu	Phe	Ser	Asn	His	Phe	Ser	Thr	Leu	Val	Tyr	Arg	Asn
			660					665					670		
Leu	Gln	Ile	Ala	Lys	Asn	Ser	Tyr	Asn	Asp	Ala	Leu	Leu	Thr	Phe	Val
		675					680					685			
Trp	Lys	Leu	Val	Ala	Asn	Phe	Arg	Arg	Gly	Phe	Arg	Lys	Glu	Asp	Arg
	690				695						700				
Asn	Gly	Arg	Asp	Glu	Met	Asp	Ile	Glu	Leu	His	Asp	Val	Ser	Pro	Ile
705					710					715					720
Thr	Arg	His	Pro	Leu	Gln	Ala	Leu	Phe	Ile	Trp	Ala	Ile	Leu	Gln	Asn
			725						730					735	
Lys	Lys	Glu	Leu	Ser	Lys	Val	Ile	Trp	Glu	Gln	Thr	Arg	Gly	Cys	Thr
		740						745					750		
Leu	Ala	Ala	Leu	Gly	Ala	Ser	Lys	Leu	Leu	Lys	Thr	Leu	Ala	Lys	Val
		755					760					765			
Lys	Asn	Asp	Ile	Asn	Ala	Ala	Gly	Glu	Ser	Glu	Glu	Leu	Ala	Asn	Glu
	770				775						780				
Tyr	Glu	Thr	Arg	Ala	Val	Glu	Leu	Phe	Thr	Glu	Cys	Tyr	Ser	Ser	Asp
785					790					795					800
Glu	Asp	Leu	Ala	Glu	Gln	Leu	Leu	Val	Tyr	Ser	Cys	Glu	Ala	Trp	Gly
			805					810						815	
Gly	Ser	Asn	Cys	Leu	Glu	Leu	Ala	Val	Glu	Ala	Thr	Asp	Gln	His	Phe
			820					825					830		
Ile	Ala	Gln	Pro	Gly	Val	Gln	Asn	Phe	Leu	Ser	Lys	Gln	Trp	Tyr	Gly
		835				840						845			
Glu	Ile	Ser	Arg	Asp	Thr	Lys	Asn	Trp	Lys	Ile	Ile	Leu	Cys	Leu	Phe
	850					855					860				
Ile	Ile	Pro	Leu	Val	Gly	Cys	Gly	Phe	Val	Ser	Phe	Arg	Lys	Lys	Pro
865					870					875					880
Val	Asp	Lys	His	Lys	Lys	Leu	Leu	Trp	Tyr	Tyr	Val	Ala	Phe	Phe	Thr
			885					890						895	
Ser	Pro	Phe	Val	Val	Phe	Ser	Trp	Asn	Val	Val	Phe	Tyr	Ile	Ala	Phe
			900					905					910		
Leu	Leu	Leu	Phe	Ala	Tyr	Val	Leu	Leu	Met	Asp	Phe	His	Ser	Val	Pro
		915					920					925			
His	Pro	Pro	Glu	Leu	Val	Leu	Tyr	Ser	Leu	Val	Phe	Val	Leu	Phe	Cys
	930					935					940				
Asp	Glu	Val	Arg	Gln	Trp	Tyr	Val	Asn	Gly	Val	Asn	Tyr	Phe	Thr	Asp
945					950					955					960
Leu	Trp	Asn	Val	Met	Asp	Thr	Leu	Gly	Leu	Phe	Tyr	Phe	Ile	Ala	Gly
			965					970						975	
Ile	Val	Phe	Arg	Leu	His	Ser	Ser	Asn	Lys	Ser	Ser	Leu	Tyr	Ser	Gly
			980					985					990		
Arg	Val	Ile	Phe	Cys	Leu	Asp	Tyr	Ile	Ile	Phe	Thr	Leu	Arg	Leu	Ile
		995					1000					1005			
His	Ile	Phe	Thr	Val	Ser	Arg	Asn	Leu	Gly	Pro	Lys	Ile	Ile	Met	Leu
	1010					1015					1020				
Gln	Arg	Met	Leu	Ile	Asp	Val	Phe	Phe	Phe	Leu	Phe	Leu	Phe	Ala	Val
1025					1030					1035					1040

Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu Arg Gln Asn
 1045 1050 1055
 Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr Glu Pro Tyr
 1060 1065 1070
 Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly Thr Thr Tyr
 1075 1080 1085
 Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys Pro Leu Cys
 1090 1095 1100
 Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu Trp Ile Thr
 1105 1110 1115 1120
 Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile Leu Leu Val
 1125 1130 1135
 Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr Val Gln Glu
 1140 1145 1150
 Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu Val Gln Glu
 1155 1160 1165
 Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val Phe Ala Tyr
 1170 1175 1180
 Phe Tyr Met Val Val Lys Cys Phe Lys Cys Cys Lys Glu Lys
 1185 1190 1195 1200
 Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp Asn Glu Thr
 1205 1210 1215
 Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val Lys Ile Asn
 1220 1225 1230
 Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg Phe Arg Gln
 1235 1240 1245
 Leu Asp Thr Lys Leu Asn Asp Leu Lys Gly Leu Leu Lys Glu Ile Ala
 1250 1255 1260
 Asn Lys Ile Lys
 1265

<210> 12

<211> 3804

<212> DNA

<213> Artificial Sequence

<220>

<223> Generic sequence that encompasses all nucleotide sequences that encode human TRPM8 having amino acid sequence as shown in SEQ ID NO:11

<221> CDS

<222> (1)...(3804)

<221> misc_feature

<222> 21,33,42,57,69,96,123,153,249,324,378,417,426,498,519,552,570,573,579,585,597,603,609,675,717,750,855,933,990,1014,1098,1104,1107,1155,1350,1371,1449,1488,1515,1545,1548,1593,1620,1656,1707,1719,1743,1749,1857,1986,2037,2154,2223,2277,2394,2397,2433,2454,2529,2553,2625,2691,2709,2778,2811,2949,2952,2961,2964,2973,3042,3198,3243,3300,3390,3513,3612,3615,3717

<223> n = A,T,C or G if after TC;
n = T or C if after AG

<221> misc_feature

<222> 39,138,201,210,288,303,306,309,321,471,504,513,525,531,534,558,582,648,849,972,978,993,1083,1101,1161,1176,1233,1326,1356,1572,1584,1596,1845,1848,1902,1917,1947,2013,2088,2091,2100,2112,2121,2166,2247,2364,2556,2631,2844,2940,2979,3018,3045,3078,3147,3162,3177,3183,3195,3342,3486,3516,3729,3735,3741

<223> n = A,T,C or G if after CG;
n = A or G if after AG

<221> misc_feature

<222> all "n" not specified above

<223> n = A,T,C or G

<400> 12

atg ccn ytn ccn cay aar wsn ggn car aar wsn ytn mgn wsn tay tty	48
Met Pro Leu Pro His Lys Ser Gly Gln Lys Ser Leu Arg Ser Tyr Phe	
1 5 10 15	
gtn tty wsn ath car gtn wsn gtn ath car ath aar ggn acn gar wsn	96
Val Phe Ser Ile Gln Val Ser Val Ile Gln Ile Lys Gly Thr Glu Ser	
20 25 30	
ccn ggn tty gcn tgg tgg gcn tty wsn ggn ccn ytn tty mgn tty ytn	144
Pro Gly Phe Ala Trp Trp Ala Phe Ser Gly Pro Leu Phe Arg Phe Leu	
35 40 45	
ccn tty wsn gtn ytn ytn gcn ytn gar ytn acn gtn gtn ytn acn ggn	192
Pro Phe Ser Val Leu Leu Ala Leu Glu Leu Thr Val Val Leu Thr Gly	
50 55 60	
gtn tgg mgn ytn ytn mgn ccn tgy tay cay tgy gtn tay tgy ggn ccn	240
Val Trp Arg Leu Leu Arg Pro Cys Tyr His Cys Val Tyr Cys Gly Pro	
65 70 75 80	
gcn gcn wsn gcn cay ytn tty ath aar car tgg ytn gay ggn tgg mgn	288
Ala Ala Ser Ala His Leu Phe Ile Lys Gln Trp Leu Asp Gly Trp Arg	
85 90 95	
atg car gtn gay mgn mgn mgn ggn gcn tgy mgn wsn aar ggn ytn gtn	336
Met Gln Val Asp Arg Arg Arg Gly Ala Cys Arg Ser Lys Gly Leu Val	
100 105 110	
car gtn gar ggn gcn acn car gcn ggn gar cay ytn ytn wsn ytn ggn	384
Gln Val Glu Gly Ala Thr Gln Ala Gly Glu His Leu Leu Ser Leu Gly	
115 120 125	
ath gtn ggn cay ytn ccn gar gar atg atg wsn gar ytn wsn ytn gar	432
Ile Val Gly His Leu Pro Glu Glu Met Met Ser Glu Leu Ser Leu Glu	
130 135 140	
gay gar car gar atg acn gcn ggn ggn gtn tgg ggn mgn ggn ytn tgg	480
Asp Glu Gln Glu Met Thr Ala Gly Gly Val Trp Gly Arg Gly Leu Trp	
145 150 155 160	
acn gar gar aar atg wsn tty mgn gcn gcn mgn ytn wsn atg mgn aay	528
Thr Glu Glu Lys Met Ser Phe Arg Ala Ala Arg Leu Ser Met Arg Asn	
165 170 175	
mgn mgn aay gay acn ytn gay wsn acn mgn acn ytn tay wsn wsn gcn	576
Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr Ser Ser Ala	
180 185 190	
wsn mgn wsn acn gay ytn wsn tay wsn gar wsn gay ytn gtn aay tty	624
Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu Val Asn Phe	
195 200 205	
ath car gcn aay tty aar aar mgn gar tgy gtn tty tty ath aar gay	672
Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe Ile Lys Asp	
210 215 220	
wsn aar gcn acn gar aay gtn tgy aar tgy ggn tay gcn car wsn car	720
Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala Gln Ser Gln	
225 230 235 240	
cay atg gar ggn acn car ath aay car wsn gar aar tgg aay tay aar	768
His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp Asn Tyr Lys	
245 250 255	
aar cay acn aar gar tty ccn acn gay gcn tty ggn gay ath car tty	816
Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp Ile Gln Phe	
260 265 270	

gar	acn	ytn	ggn	aar	aar	ggn	aar	tay	ath	mgn	ytn	wsn	tgy	gay	acn	864
Glu	Thr	Leu	Gly	Lys	Lys	Gly	Lys	Tyr	Ile	Arg	Leu	Ser	Cys	Asp	Thr	
		275					280					285				
gay	gcn	gar	ath	ytn	tay	gar	ytn	ytn	acn	car	cay	tgg	cay	ytn	aar	912
Asp	Ala	Glu	Ile	Leu	Tyr	Glu	Leu	Leu	Thr	Gln	His	Trp	His	Leu	Lys	
	290					295					300					
acn	ccn	aay	ytn	gtn	ath	wsn	gtn	acn	ggn	ggn	gcn	aar	aay	tty	gcn	960
Thr	Pro	Asn	Leu	Val	Ile	Ser	Val	Thr	Gly	Gly	Ala	Lys	Asn	Phe	Ala	
305					310					315					320	
ytn	aar	ccn	mgn	atg	mgn	aar	ath	tty	wsn	mgn	ytn	ath	tay	ath	gcn	1008
Leu	Lys	Pro	Arg	Met	Arg	Lys	Ile	Phe	Ser	Arg	Leu	Ile	Tyr	Ile	Ala	
				325					330					335		
car	wsn	aar	ggn	gcn	tgg	ath	ytn	acn	ggn	ggn	acn	cay	tay	ggn	ytn	1056
Gln	Ser	Lys	Gly	Ala	Trp	Ile	Leu	Thr	Gly	Gly	Thr	His	Tyr	Gly	Leu	
			340					345					350			
atg	aar	tay	ath	ggn	gar	gtn	gtn	mgn	gay	aay	acn	ath	wsn	mgn	wsn	1104
Met	Lys	Tyr	Ile	Gly	Glu	Val	Val	Arg	Asp	Asn	Thr	Ile	Ser	Arg	Ser	
		355					360					365				
wsn	gar	gar	aay	ath	gtn	gcn	ath	ggn	ath	gcn	gcn	tgg	ggn	atg	gtn	1152
Ser	Glu	Glu	Asn	Ile	Val	Ala	Ile	Gly	Ile	Ala	Ala	Trp	Gly	Met	Val	
	370					375					380					
wsn	aay	mgn	gay	acn	ytn	ath	mgn	aay	tgy	gay	gcn	gar	ggn	tay	tty	1200
Ser	Asn	Arg	Asp	Thr	Leu	Ile	Arg	Asn	Cys	Asp	Ala	Glu	Gly	Tyr	Phe	
385					390				395						400	
ytn	gcn	car	tay	ytn	atg	gay	gay	tty	acn	mgn	gay	ccn	ytn	tay	ath	1248
Leu	Ala	Gln	Tyr	Leu	Met	Asp	Asp	Phe	Thr	Arg	Asp	Pro	Leu	Tyr	Ile	
				405				410						415		
ytn	gay	aay	aay	cay	acn	cay	ytn	ytn	ytn	gtn	gay	aay	ggn	tgy	cay	1296
Leu	Asp	Asn	Asn	His	Thr	His	Leu	Leu	Leu	Val	Asp	Asn	Gly	Cys	His	
			420					425					430			
ggn	cay	ccn	acn	gtn	gar	gcn	aar	ytn	mgn	aay	car	ytn	gar	aar	tay	1344
Gly	His	Pro	Thr	Val	Glu	Ala	Lys	Leu	Arg	Asn	Gln	Leu	Glu	Lys	Tyr	
		435					440					445				
ath	wsn	gar	mgn	acn	ath	car	gay	wsn	aay	tay	ggn	ggn	aar	ath	ccn	1392
Ile	Ser	Glu	Arg	Thr	Ile	Gln	Asp	Ser	Asn	Tyr	Gly	Gly	Lys	Ile	Pro	
	450					455					460					
ath	gtn	tgy	tty	gcn	car	ggn	ggn	ggn	aar	gar	acn	ytn	aar	gcn	ath	1440
Ile	Val	Cys	Phe	Ala	Gln	Gly	Gly	Gly	Lys	Glu	Thr	Leu	Lys	Ala	Ile	
465					470					475					480	
aay	acn	wsn	ath	aar	aay	aar	ath	ccn	tgy	gtn	gtn	gtn	gar	ggn	wsn	1488
Asn	Thr	Ser	Ile	Lys	Asn	Lys	Ile	Pro	Cys	Val	Val	Val	Glu	Gly	Ser	
				485					490					495		
ggn	car	ath	gcn	gay	gtn	ath	gcn	wsn	ytn	gtn	gar	gtn	gar	gay	gcn	1536
Gly	Gln	Ile	Ala	Asp	Val	Ile	Ala	Ser	Leu	Val	Glu	Val	Glu	Asp	Ala	
			500					505					510			
ytn	acn	wsn	wsn	gcn	gtn	aar	gar	aar	ytn	gtn	mgn	tty	ytn	ccn	mgn	1584
Leu	Thr	Ser	Ser	Ala	Val	Lys	Glu	Lys	Leu	Val	Arg	Phe	Leu	Pro	Arg	
			515				520					525				
acn	gtn	wsn	mgn	ytn	ccn	gar	gar	gar	acn	gar	wsn	tgg	ath	aar	tgg	1632
Thr	Val	Ser	Arg	Leu	Pro	Glu	Glu	Glu	Thr	Glu	Ser	Trp	Ile	Lys	Trp	
	530					535					540					

ytn Leu 545	aar Lys	gar Glu	ath Ile	ytn Leu	gar Glu 550	tgy Cys	wsn Ser	cay His	ytn Leu	ytn Leu 555	acn Thr	gtn Val	ath Ile	aar Lys	atg Met 560	1680
gar Glu	gar Glu	gcn Ala	ggn Gly	gay Asp 565	gar Glu	ath Ile	gtn Val	wsn Ser	aay Asn 570	gcn Ala	ath Ile	wsn Ser	tay Tyr	gcn Ala 575	ytn Leu	1728
tay Tyr	aar Lys	gcn Ala	tty Phe 580	wsn Ser	acn Thr	wsn Ser	gar Glu	car Gln 585	gay Asp	aar Lys	gay Asp	aay Asn	tgg Trp 590	aay Asn	ggn Gly	1776
car Gln	ytn Leu	aar Lys 595	ytn Leu	ytn Leu	ytn Leu	gar Glu	tgg Trp 600	aay Asn	car Gln	ytn Leu	gay Asp	ytn Leu	gcn Ala 605	aay Asn	gay Asp	1824
gar Glu	ath Ile 610	tty Phe	acn Thr	aay Asn	gay Asp	mgn Arg 615	mgn Arg	tgg Trp	gar Glu	wsn Ser	gcn Ala 620	gay Asp	ytn Leu	car Gln	gar Glu	1872
gtn Val 625	atg Met	tty Phe	acn Thr	gcn Ala	ytn Leu 630	ath Ile	aar Lys	gay Asp	mgn Arg 635	ccn Pro	aar Lys	tty Phe	gtn Val	mgn Arg	ytn Leu 640	1920
tty Phe	ytn Leu	gar Glu	aay Asn	ggn Gly 645	ytn Leu	aay Asn	ytn Leu	mgn Arg 650	aar Lys	tty Phe	ytn Leu	acn Thr	cay His	gay Asp 655	gtn Val	1968
ytn Leu	acn Thr	gar Glu	ytn Leu 660	tty Phe	wsn Ser	aay Asn	cay His	tty Phe 665	wsn Ser	acn Thr	ytn Leu	gtn Val	tay Tyr 670	mgn Arg	aay Asn	2016
ytn Leu	car Gln	ath Ile 675	gcn Ala	aar Lys	aay Asn	wsn Ser	tay Tyr 680	aay Asn	gay Asp	gcn Ala	ytn Leu	ytn Leu 685	acn Thr	tty Phe	gtn Val	2064
tgg Trp	aar Lys 690	ytn Leu	gtn Val	gcn Ala	aay Asn	tty Phe 695	mgn Arg	mgn Arg	ggn Gly	tty Phe	mgn Arg 700	aar Lys	gar Glu	gay Asp	mgn Arg	2112
aay Asn 705	ggn Gly	mgn Arg	gay Asp	gar Glu	atg Met 710	gay Asp	ath Ile	gar Glu	ytn Leu	cay His 715	gay Asp	gtn Val	wsn Ser	ccn Pro	ath Ile 720	2160
acn Thr	mgn Arg	cay His	ccn Pro	ytn Leu 725	car Gln	gcn Ala	ytn Leu	tty Phe 730	ath Ile	tgg Trp	gcn Ala	ath Ile	ytn Leu	car Gln 735	aay Asn	2208
aar Lys	aar Lys	gar Glu	ytn Leu 740	wsn Ser	aar Lys	gtn Val	ath Ile	tgg Trp 745	gar Glu	car Gln	acn Thr	mgn Arg	ggn Gly 750	tgy Cys	acn Thr	2256
ytn Leu	gcn Ala	gcn Ala 755	ytn Leu	ggn Gly	gcn Ala	wsn Ser	aar Lys 760	ytn Leu	ytn Leu	aar Lys	acn Thr	ytn Leu 765	gcn Ala	aar Lys	gtn Val	2304
aar Lys	aay Asn 770	gay Asp	ath Ile	aay Asn	gcn Ala	gcn Ala 775	ggn Gly	gar Glu	wsn Ser	gar Glu	gar Glu 780	ytn Leu	gcn Ala	aay Asn	gar Glu	2352
tay Tyr 785	gar Glu	acn Thr	mgn Arg	gcn Ala	gtn Val 790	gar Glu	ytn Leu	tty Phe	acn Thr	gar Glu 795	tgy Cys	tay Tyr	wsn Ser	wsn Ser	gay Asp 800	2400
gar Glu	gay Asp	ytn Leu	gcn Ala	gar Glu 805	car Gln	ytn Leu	ytn Leu	gtn Val	tay Tyr 810	wsn Ser	tgy Cys	gar Glu	gcn Ala	tgg Trp 815	ggn Gly	2448

ggn wsn aay tgy ytn gar ytn gcn gtn gar gcn acn gay car cay tty	2496
Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp Gln His Phe	
820 825 830	
ath gcn car ccn ggn gtn car aay tty ytn wsn aar car tgg tay ggn	2544
Ile Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln Trp Tyr Gly	
835 840 845	
gar ath wsn mgn gay acn aar aay tgg aar ath ath ytn tgy ytn tty	2592
Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu Cys Leu Phe	
850 855 860	
ath ath ccn ytn gtn ggn tgy ggn tty gtn wsn tty mgn aar aar ccn	2640
Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg Lys Lys Pro	
865 870 875 880	
gtn gay aar cay aar aar ytn ytn tgg tay tay gtn gcn tty tty acn	2688
Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala Phe Thr	
885 890 895	
wsn ccn tty gtn gtn tty wsn tgg aay gtn gtn tty tay ath gcn tty	2736
Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr Ile Ala Phe	
900 905 910	
ytn ytn ytn tty gcn tay gtn ytn ytn atg gay tty cay wsn gtn ccn	2784
Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His Ser Val Pro	
915 920 925	
cay ccn ccn gar ytn gtn ytn tay wsn ytn gtn tty gtn ytn tty tgy	2832
His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val Leu Phe Cys	
930 935 940	
gay gar gtn mgn car tgg tay gtn aay ggn gtn aay tay tty acn gay	2880
Asp Glu Val Arg Gln Trp Tyr Val Asn Gly Val Asn Tyr Phe Thr Asp	
945 950 955 960	
ytn tgg aay gtn atg gay acn ytn ggn ytn tty tay tty ath gcn ggn	2928
Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe Ile Ala Gly	
965 970 975	
ath gtn tty mgn ytn cay wsn wsn aay aar wsn wsn ytn tay wsn ggn	2976
Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu Tyr Ser Gly	
980 985 990	
mgn gtn ath tty tgy ytn gay tay ath ath tty acn ytn mgn ytn ath	3024
Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu Arg Leu Ile	
995 1000 1005	
cay ath tty acn gtn wsn mgn aay ytn ggn ccn aar ath ath atg ytn	3072
His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile Ile Met Leu	
1010 1015 1020	
car mgn atg ytn ath gay gtn tty tty tty ytn tty ytn tty gcn gtn	3120
Gln Arg Met Leu Ile Asp Val Phe Phe Phe Leu Phe Leu Phe Ala Val	
1025 1030 1035 1040	
tgg atg gtn gcn tty ggn gtn gcn mgn car ggn ath ytn mgn car aay	3168
Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu Arg Gln Asn	
1045 1050 1055	
gar car mgn tgg mgn tgg ath tty mgn wsn gtn ath tay gar ccn tay	3216
Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr Glu Pro Tyr	
1060 1065 1070	
ytn gcn atg tty ggn car gtn ccn wsn gay gtn gay ggn acn acn tay	3264
Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly Thr Thr Tyr	
1075 1080 1085	

gay tty gcn cay tgy acn tty acn ggn aay gar wsn aar ccn ytn tgy 3312
 Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys Pro Leu Cys
 1090 1095 1100

gtn gar ytn gay gar cay aay ytn ccn mgn tty ccn gar tgg ath acn 3360
 Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu Trp Ile Thr
 1105 1110 1115 1120

ath ccn ytn gtn tgy ath tay atg ytn wsn acn aay ath ytn ytn gtn 3408
 Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile Leu Leu Val
 1125 1130 1135

aay ytn ytn gtn gcn atg tty ggn tay acn gtn ggn acn gtn car gar 3456
 Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr Val Gln Glu
 1140 1145 1150

aay aay gay car gtn tgg aar tty car mgn tay tty ytn gtn car gar 3504
 Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu Val Gln Glu
 1155 1160 1165

tay tgy wsn mgn ytn aay ath ccn tty ccn tty ath gtn tty gcn tay 3552
 Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val Phe Ala Tyr
 1170 1175 1180

tty tay atg gtn gtn aar aar tgy tty aar tgy tgy tgy aar gar aar 3600
 Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys Lys Glu Lys
 1185 1190 1195 1200

aay atg gar wsn wsn gtn tgy tgy tty aar aay gar gay aay gar acn 3648
 Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp Asn Glu Thr
 1205 1210 1215

ytn gcn tgg gar ggn gtn atg aar gar aay tay ytn gtn aar ath aay 3696
 Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val Lys Ile Asn
 1220 1225 1230

acn aar gcn aay gay acn wsn gar gar atg mgn cay mgn tty mgn car 3744
 Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg Phe Arg Gln
 1235 1240 1245

ytn gay acn aar ytn aay gay ytn aar ggn ytn ytn aar gar ath gcn 3792
 Leu Asp Thr Lys Leu Asn Asp Leu Lys Gly Leu Leu Lys Glu Ile Ala
 1250 1255 1260

aay aar ath aar 3804
 Asn Lys Ile Lys
 1265

<210> 13
 <211> 3281
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (156)... (2771)

<400> 13
 ctaatacgac tcactatagg gcaagcagtg gtaacaacgc agagtacgcg ggggaagcgc 60
 agcaggagga ggacgcggcc ggagggatca ggaagcggcg gcgctgcgcc cgcgtcctga 120
 gcaggccgag aagtacaaac agatctgggt ccagt atg gca gat cct ggt gat 173
 Met Ala Asp Pro Gly Asp
 1 5

ggt ccc cgt gca gcg cct ggg gag gtg gct gag ccc cct gga gat gag 221
 Gly Pro Arg Ala Ala Pro Gly Glu Val Ala Glu Pro Pro Gly Asp Glu

42/75

10				15				20								
agt Ser	ggt Gly	acc Thr 25	tct Ser	ggt Gly	ggg Gly	gag Glu	gcc Ala 30	ttc Phe	ccc Pro	ctc Leu	tct Ser	tcc Ser 35	ctg Leu	gcc Ala	aat Asn	269
ctg Leu	ttt Phe 40	gag Glu	ggg Gly	gag Glu	gaa Glu	ggc Gly 45	tcc Ser	tct Ser	tct Ser	ctt Leu	tcc Ser 50	ccg Pro	gtg Val	gat Asp	gct Ala	317
agc Ser 55	cgc Arg	cct Pro	gct Ala	ggc Gly	cct Pro 60	ggc Gly	gat Asp	gga Gly	cgt Arg	cca Pro 65	aac Asn	ctg Leu	cgt Arg	atg Met	aag Lys 70	365
ttc Phe	cag Gln	ggc Gly	gct Ala	ttc Phe 75	cgc Arg	aag Lys	ggg Gly	gtt Val	ccc Pro 80	aac Asn	ccc Pro	att Ile	gac Asp	ctg Leu 85	ttg Leu	413
gag Glu	tcc Ser	acc Thr	ctg Leu 90	tac Tyr	gag Glu	tcc Ser	tca Ser	gta Val 95	gtg Val	cct Pro	ggg Gly	ccc Pro	aag Lys 100	aaa Lys	gcg Ala	461
ccc Pro	atg Met	gat Asp 105	tcc Ser	ttg Leu	ttc Phe	gac Asp	tac Tyr 110	ggc Gly	act Thr	tac Tyr	cgt Arg	cac His 115	cac His	ccc Pro	agt Ser	509
gac Asp	aac Asn 120	aag Lys	aga Arg	tgg Trp	agg Arg	aga Arg 125	aag Lys	gtc Val	gtg Val	gag Glu	aag Lys 130	cag Gln	cca Pro	cag Gln	agc Ser	557
ccc Pro 135	aaa Lys	gct Ala	cct Pro	gca Ala	ccc Pro 140	cag Gln	cca Pro	ccc Pro	ccc Pro	atc Ile 145	ctc Leu	aaa Lys	gtc Val	ttc Phe	aat Asn 150	605
cgg Arg	ccc Pro	atc Ile	ctc Leu	ttt Phe 155	gac Asp	att Ile	gtg Val	tcc Ser	cgg Arg 160	ggc Gly	tcc Ser	act Thr	gcg Ala	gac Asp 165	cta Leu	653
gat Asp	gga Gly	ctg Leu	ctc Leu 170	tcc Ser	ttc Phe	ttg Leu	ttg Leu	acc Thr 175	cac His	aag Lys	aag Lys	cgc Arg	ctg Leu 180	act Thr	gat Asp	701
gag Glu	gag Glu	ttc Phe 185	cgg Arg	gag Glu	ccg Pro	tcc Ser	acg Thr 190	ggg Gly	aag Lys	acc Thr	tgc Cys	ctg Leu 195	ccc Pro	aag Lys	gcg Ala	749
ctg Leu	ctg Leu 200	aac Asn	cta Leu	agc Ser	aac Asn	ggg Gly 205	cgc Arg	aac Asn	gac Asp	acc Thr	atc Ile 210	ccg Pro	gtg Val	ttg Leu	ctg Leu	797
gac Asp 215	att Ile	gcg Ala	gag Glu	cgc Arg	acc Thr 220	ggc Gly	aac Asn	atg Met	cgt Arg	gaa Glu 225	ttc Phe	atc Ile	aac Asn	tcg Ser	ccc Pro 230	845
ttc Phe	aga Arg	gac Asp	atc Ile	tac Tyr 235	tac Tyr	cga Arg	ggc Gly	cag Gln	aca Thr 240	tcc Ser	ctg Leu	cac His	att Ile	gcc Ala 245	atc Ile	893
gaa Glu	cgg Arg	cgc Arg	tgc Cys 250	aag Lys	cac His	tac Tyr	gtg Val	gag Glu 255	ctg Leu	ctg Leu	gtg Val	gcc Ala 260	cag Gln	gga Gly	gcc Ala	941
gac Asp	gtg Val	cac His 265	gcc Ala	cag Gln	gcc Ala	cgc Arg	ggc Gly 270	cgc Arg	ttc Phe	ttc Phe	cag Gln	ccc Pro 275	aag Lys	gat Asp	gag Glu	989
gga Gly	ggc Gly	tac Tyr	ttc Phe	tac Tyr	ttt Phe	ggg Gly	gag Glu	ctg Leu	ccc Pro	ttg Leu	tcc Ser	ctg Leu	gca Ala	gcc Ala	tgc Cys	1037

280					285					290						
acc Thr 295	aac Asn	cag Gln	ccg Pro	cac His	atc Ile 300	gtc Val	aac Asn	tac Tyr	ctg Leu	aca Thr 305	gag Glu	aac Asn	cct Pro	cac His	aag Lys 310	1085
aaa Lys	gct Ala	gac Asp	atg Met	agg Arg 315	cga Arg	cag Gln	gac Asp	tcg Ser	agg Arg 320	ggg Gly	aac Asn	acg Thr	gtg Val	ctg Leu 325	cac His	1133
gcg Ala	ctg Leu	gtg Val	gcc Ala 330	atc Ile	gcc Ala	gac Asp	aac Asn	acc Thr 335	cga Arg	gag Glu	aac Asn	acc Thr	aag Lys 340	ttt Phe	gtc Val	1181
acc Thr	aag Lys	atg Met 345	tac Tyr	gac Asp	ctg Leu	ctg Leu	ctt Leu 350	ctc Leu	aag Lys	tgt Cys	tca Ser	cgc Arg 355	ctc Leu	ttc Phe	ctc Leu	1229
gac Asp	agc Ser 360	aac Asn	ctg Leu	gag Glu	aca Thr	gtt Val 365	ctc Leu	aac Asn	aat Asn	gat Asp	ggc Gly 370	ctt Leu	tcg Ser	cct Pro	ctc Leu	1277
atg Met 375	atg Met	gct Ala	gcc Ala	aag Lys	aca Thr 380	ggc Gly	aag Lys	atc Ile	ggg Gly	gtc Val 385	ttt Phe	cag Gln	cac His	atc Ile	atc Ile 390	1325
cga Arg	cgt Arg	gag Glu	gtg Val	aca Thr 395	gat Asp	gag Glu	gac Asp	acc Thr	cgg Arg 400	cat His	ctg Leu	tct Ser	cgc Arg	aag Lys 405	ttc Phe	1373
aag Lys	gac Asp	tgg Trp	gcc Ala 410	tat Tyr	ggg Gly	cct Pro	gtg Val	tat Tyr 415	tct Ser	tct Ser	ctc Leu	tac Tyr	gac Asp 420	ctc Leu	tcc Ser	1421
tcc Ser	ctg Leu	gac Asp 425	aca Thr	tgc Cys	ggg Gly	gag Glu	gag Glu 430	gtg Val	tcc Ser	gtg Val	ctg Leu	gag Glu 435	atc Ile	ctg Leu	gtg Val	1469
tac Tyr	aac Asn 440	agc Ser	aag Lys	atc Ile	gag Glu	aac Asn 445	cgc Arg	cat His	gag Glu	atg Met	ctg Leu 450	gct Ala	gta Val	gag Glu	ccc Pro	1517
att Ile 455	aac Asn	gaa Glu	ctg Leu	ttg Leu	aga Arg 460	gac Asp	aag Lys	tgg Trp	cgt Arg	aag Lys 465	ttt Phe	ggg Gly	gct Ala	gtg Val	tcc Ser 470	1565
ttc Phe	tac Tyr	atc Ile	aac Asn	gtg Val 475	gtc Val	tcc Ser	tat Tyr	ctg Leu	tgt Cys 480	gcc Ala	atg Met	gtc Val	atc Ile	ttc Phe 485	acc Thr	1613
ctc Leu	acc Thr	gcc Ala	tac Tyr 490	tat Tyr	cag Gln	cca Pro	ctg Leu	gag Glu 495	ggc Gly	acg Thr	cca Pro	ccc Pro	tac Tyr 500	cct Pro	tac Tyr	1661
cgg Arg	acc Thr	aca Thr 505	gtg Val	gac Asp	tac Tyr	ctg Leu	agg Arg 510	ctg Leu	gct Ala	ggc Gly	gag Glu	gtc Val 515	atc Ile	acg Thr	ctc Leu	1709
ttc Phe	aca Thr 520	gga Gly	gtc Val	ctg Leu	ttc Phe	ttc Phe 525	ttt Phe	acc Thr	agt Ser	atc Ile	aaa Lys 530	gac Asp	ttg Leu	ttc Phe	acg Thr	1757
aag Lys 535	aaa Lys	tgc Cys	cct Pro	gga Gly	gtg Val 540	aat Asn	tct Ser	ctc Leu	ttc Phe	gtc Val 545	gat Asp	ggc Gly	tcc Ser	ttc Phe	cag Gln 550	1805
tta Leu	ctc Leu	tac Tyr	ttc Phe	atc Ile	tac Tyr	tct Ser	gtg Val	ctg Leu	gtg Val	gtt Val	gtc Val	tct Ser	gcg Ala	gcg Ala	ctc Leu	1853

																	44/75
555								560					565				
tac	ctg	gct	ggg	atc	gag	gcc	tac	ctg	gct	gtg	atg	gtc	ttt	gcc	ctg	1901	
Tyr	Leu	Ala	Gly	Ile	Glu	Ala	Tyr	Leu	Ala	Val	Met	Val	Phe	Ala	Leu		
			570							575				580			
gtc	ctg	ggc	tgg	atg	aat	gcg	ctg	tac	ttc	acg	cgc	ggg	ttg	aag	ctg	1949	
Val	Leu	Gly	Trp	Met	Asn	Ala	Leu	Tyr	Phe	Thr	Arg	Gly	Leu	Lys	Leu		
			585							590				595			
acg	ggg	acc	tac	agc	atc	atg	att	cag	aag	atc	ctc	ttc	aaa	gac	ctc	1997	
Thr	Gly	Thr	Tyr	Ser	Ile	Met	Ile	Gln	Lys	Ile	Leu	Phe	Lys	Asp	Leu		
			600							605				610			
ttc	cgc	ttc	ctg	ctt	gtg	tac	ctg	ctc	ttc	atg	atc	ggc	tat	gcc	tca	2045	
Phe	Arg	Phe	Leu	Leu	Val	Tyr	Leu	Leu	Phe	Met	Ile	Gly	Tyr	Ala	Ser		
			615							620				625			
gcc	ctg	gtc	acc	ctc	ctg	aat	ccg	tgc	acc	aac	atg	aag	gtc	tgt	gac	2093	
Ala	Leu	Val	Thr	Leu	Leu	Asn	Pro	Cys	Thr	Asn	Met	Lys	Val	Cys	Asp		
			635							640				645			
gag	gac	cag	agc	aac	tgc	acg	gtg	ccc	acg	tat	cct	gcg	tgc	cgc	gac	2141	
Glu	Asp	Gln	Ser	Asn	Cys	Thr	Val	Pro	Thr	Tyr	Pro	Ala	Cys	Arg	Asp		
			650							655				660			
agc	gag	acc	ttc	agc	gcc	ttc	ctc	ctg	gac	ctc	ttc	aag	ctc	acc	atc	2189	
Ser	Glu	Thr	Phe	Ser	Ala	Phe	Leu	Leu	Asp	Leu	Phe	Lys	Leu	Thr	Ile		
			665							670				675			
ggc	atg	gga	gac	ctg	gag	atg	ctg	agc	agc	gcc	aag	tac	ccc	gtg	gtc	2237	
Gly	Met	Gly	Asp	Leu	Glu	Met	Leu	Ser	Ser	Ala	Lys	Tyr	Pro	Val	Val		
			680							685				690			
ttc	atc	ctc	ctg	ctg	gtc	acc	tac	atc	atc	ctc	acc	ttc	gtg	ctc	ctg	2285	
Phe	Ile	Leu	Leu	Leu	Val	Thr	Tyr	Ile	Ile	Leu	Thr	Phe	Val	Leu	Leu		
			695							700				705			
ttg	aac	atg	ctt	atc	gcc	ctc	atg	ggt	gag	acc	gtg	ggc	cag	gtg	tcc	2333	
Leu	Asn	Met	Leu	Ile	Ala	Leu	Met	Gly	Glu	Thr	Val	Gly	Gln	Val	Ser		
			715							720				725			
aag	gag	agc	aag	cac	atc	tgg	aag	ttg	cag	tgg	gcc	acc	acc	atc	ctg	2381	
Lys	Glu	Ser	Lys	His	Ile	Trp	Lys	Leu	Gln	Trp	Ala	Thr	Thr	Ile	Leu		
			730							735				740			
gac	atc	gag	cgt	tcc	ttc	cct	gtg	ttc	ctg	agg	aag	gcc	ttc	cgc	tcc	2429	
Asp	Ile	Glu	Arg	Ser	Phe	Pro	Val	Phe	Leu	Arg	Lys	Ala	Phe	Arg	Ser		
			745							750				755			
gga	gag	atg	gtg	act	gtg	ggc	aag	agc	tca	gat	ggc	act	ccg	gac	cgc	2477	
Gly	Glu	Met	Val	Thr	Val	Gly	Lys	Ser	Ser	Asp	Gly	Thr	Pro	Asp	Arg		
			760							765				770			
agg	tgg	tgc	ttc	agg	gtg	gac	gag	gtg	aac	tgg	tct	cac	tgg	aac	cag	2525	
Arg	Trp	Cys	Phe	Arg	Val	Asp	Glu	Val	Asn	Trp	Ser	His	Trp	Asn	Gln		
			775							780				785			
aac	ttg	ggc	atc	att	aac	gag	gac	cct	ggc	aag	agt	gaa	atc	tac	cag	2573	
Asn	Leu	Gly	Ile	Ile	Asn	Glu	Asp	Pro	Gly	Lys	Ser	Glu	Ile	Tyr	Gln		
			795							800				805			
tac	tat	ggc	ttc	tcc	cac	acc	gtg	ggg	cgc	ctt	cgt	agg	gat	cgt	tgg	2621	
Tyr	Tyr	Gly	Phe	Ser	His	Thr	Val	Gly	Arg	Leu	Arg	Arg	Asp	Arg	Trp		
			810							815				820			
tcc	tcg	gtg	gtg	ccc	cgc	gta	gtg	gag	ctg	aac	aag	aac	tca	agc	gca	2669	
Ser	Ser	Val	Val	Pro	Arg	Val	Val	Glu	Leu	Asn	Lys	Asn	Ser	Ser	Ala		

45/75

825	830	835	
gat gaa gtg gtg gta ccc ctg gat aac cta ggg aac ccc aac tgt gac			2717
Asp Glu Val Val Val Pro Leu Asp Asn Leu Gly Asn Pro Asn Cys Asp			
840	845	850	
ggc cac cag cag ggc tac gct ccc aag tgg agg acg gac gat gcc cca			2765
Gly His Gln Gln Gly Tyr Ala Pro Lys Trp Arg Thr Asp Asp Ala Pro			
855	860	865	870
ctg tag gggccgtgcc agagctcgca cagatagtcc aggcttggcc ttcgctccca			2821
Leu *			

cctacattta ggcatttgtc cgggtgtcttc cccacccgca tgggaccttg gaggtgaggg	2881
cctctgtggc gactctgtgg agggcccagg accctctggt ccccgccaag acttttgcct	2941
tcagctctac tcccacatg gggggggcgg ggctcctggc tacctktctc gctcgtccc	3001
atggagtcac ctaagccagc acaaggcccc tctcctcgaa aggctcaggc cccatccctc	3061
ttgtgtatta tttattgtc tcctcaggaa aatggggtgg caggagtcca cccgcggctg	3121
gaacctggcc agggctgaag ctcatgcagg gacgctgcag ctccgacctg ccacagatct	3181
gacctgctgc agccctggct agtgtgggtc ttctgtactt tgaagagatc ggggcccgtg	3241
gtgctcaata aatgtttatt ctcggtggaa aaaaaaaaaa	3281

<210> 14

<211> 871

<212> PRT

<213> Mus musculus

<400> 14

Met Ala Asp Pro Gly Asp Gly Pro Arg Ala Ala Pro Gly Glu Val Ala	
1 5 10 15	
Glu Pro Pro Gly Asp Glu Ser Gly Thr Ser Gly Gly Glu Ala Phe Pro	
20 25 30	
Leu Ser Ser Leu Ala Asn Leu Phe Glu Gly Glu Glu Gly Ser Ser Ser	
35 40 45	
Leu Ser Pro Val Asp Ala Ser Arg Pro Ala Gly Pro Gly Asp Gly Arg	
50 55 60	
Pro Asn Leu Arg Met Lys Phe Gln Gly Ala Phe Arg Lys Gly Val Pro	
65 70 75 80	
Asn Pro Ile Asp Leu Glu Ser Thr Leu Tyr Glu Ser Ser Val Val	
85 90 95	
Pro Gly Pro Lys Lys Ala Pro Met Asp Ser Leu Phe Asp Tyr Gly Thr	
100 105 110	
Tyr Arg His His Pro Ser Asp Asn Lys Arg Trp Arg Arg Lys Val Val	
115 120 125	
Glu Lys Gln Pro Gln Ser Pro Lys Ala Pro Ala Pro Gln Pro Pro Pro	
130 135 140	
Ile Leu Lys Val Phe Asn Arg Pro Ile Leu Phe Asp Ile Val Ser Arg	
145 150 155 160	
Gly Ser Thr Ala Asp Leu Asp Gly Leu Leu Ser Phe Leu Leu Thr His	
165 170 175	
Lys Lys Arg Leu Thr Asp Glu Glu Phe Arg Glu Pro Ser Thr Gly Lys	
180 185 190	
Thr Cys Leu Pro Lys Ala Leu Leu Asn Leu Ser Asn Gly Arg Asn Asp	
195 200 205	
Thr Ile Pro Val Leu Leu Asp Ile Ala Glu Arg Thr Gly Asn Met Arg	
210 215 220	
Glu Phe Ile Asn Ser Pro Phe Arg Asp Ile Tyr Arg Gly Gln Thr	
225 230 235 240	
Ser Leu His Ile Ala Ile Glu Arg Arg Cys Lys His Tyr Val Glu Leu	
245 250 255	
Leu Val Ala Gln Gly Ala Asp Val His Ala Gln Ala Arg Gly Arg Phe	
260 265 270	
Phe Gln Pro Lys Asp Glu Gly Gly Tyr Phe Tyr Phe Gly Glu Leu Pro	
275 280 285	
Leu Ser Leu Ala Ala Cys Thr Asn Gln Pro His Ile Val Asn Tyr Leu	
290 295 300	
Thr Glu Asn Pro His Lys Lys Ala Asp Met Arg Arg Gln Asp Ser Arg	

305					310					315					320
Gly	Asn	Thr	Val	Leu	His	Ala	Leu	Val	Ala	Ile	Ala	Asp	Asn	Thr	Arg
				325					330						335
Glu	Asn	Thr	Lys	Phe	Val	Thr	Lys	Met	Tyr	Asp	Leu	Leu	Leu	Leu	Lys
			340					345					350		
Cys	Ser	Arg	Leu	Phe	Leu	Asp	Ser	Asn	Leu	Glu	Thr	Val	Leu	Asn	Asn
		355					360					365			
Asp	Gly	Leu	Ser	Pro	Leu	Met	Met	Ala	Ala	Lys	Thr	Gly	Lys	Ile	Gly
	370					375					380				
Val	Phe	Gln	His	Ile	Ile	Arg	Arg	Glu	Val	Thr	Asp	Glu	Asp	Thr	Arg
385					390					395					400
His	Leu	Ser	Arg	Lys	Phe	Lys	Asp	Trp	Ala	Tyr	Gly	Pro	Val	Tyr	Ser
			405					410						415	
Ser	Leu	Tyr	Asp	Leu	Ser	Ser	Leu	Asp	Thr	Cys	Gly	Glu	Glu	Val	Ser
			420					425					430		
Val	Leu	Glu	Ile	Leu	Val	Tyr	Asn	Ser	Lys	Ile	Glu	Asn	Arg	His	Glu
		435					440					445			
Met	Leu	Ala	Val	Glu	Pro	Ile	Asn	Glu	Leu	Leu	Arg	Asp	Lys	Trp	Arg
	450					455					460				
Lys	Phe	Gly	Ala	Val	Ser	Phe	Tyr	Ile	Asn	Val	Val	Ser	Tyr	Leu	Cys
465					470				475					480	
Ala	Met	Val	Ile	Phe	Thr	Leu	Thr	Ala	Tyr	Tyr	Gln	Pro	Leu	Glu	Gly
			485					490						495	
Thr	Pro	Pro	Tyr	Pro	Tyr	Arg	Thr	Thr	Val	Asp	Tyr	Leu	Arg	Leu	Ala
			500					505					510		
Gly	Glu	Val	Ile	Thr	Leu	Phe	Thr	Gly	Val	Leu	Phe	Phe	Phe	Thr	Ser
		515					520					525			
Ile	Lys	Asp	Leu	Phe	Thr	Lys	Lys	Cys	Pro	Gly	Val	Asn	Ser	Leu	Phe
	530					535					540				
Val	Asp	Gly	Ser	Phe	Gln	Leu	Leu	Tyr	Phe	Ile	Tyr	Ser	Val	Leu	Val
545					550				555					560	
Val	Val	Ser	Ala	Ala	Leu	Tyr	Leu	Ala	Gly	Ile	Glu	Ala	Tyr	Leu	Ala
			565					570						575	
Val	Met	Val	Phe	Ala	Leu	Val	Leu	Gly	Trp	Met	Asn	Ala	Leu	Tyr	Phe
			580					585					590		
Thr	Arg	Gly	Leu	Lys	Leu	Thr	Gly	Thr	Tyr	Ser	Ile	Met	Ile	Gln	Lys
		595					600					605			
Ile	Leu	Phe	Lys	Asp	Leu	Phe	Arg	Phe	Leu	Leu	Val	Tyr	Leu	Leu	Phe
	610					615					620				
Met	Ile	Gly	Tyr	Ala	Ser	Ala	Leu	Val	Thr	Leu	Leu	Asn	Pro	Cys	Thr
625					630				635					640	
Asn	Met	Lys	Val	Cys	Asp	Glu	Asp	Gln	Ser	Asn	Cys	Thr	Val	Pro	Thr
			645					650						655	
Tyr	Pro	Ala	Cys	Arg	Asp	Ser	Glu	Thr	Phe	Ser	Ala	Phe	Leu	Leu	Asp
		660						665					670		
Leu	Phe	Lys	Leu	Thr	Ile	Gly	Met	Gly	Asp	Leu	Glu	Met	Leu	Ser	Ser
		675				680						685			
Ala	Lys	Tyr	Pro	Val	Val	Phe	Ile	Leu	Leu	Leu	Val	Thr	Tyr	Ile	Ile
	690					695					700				
Leu	Thr	Phe	Val	Leu	Leu	Leu	Asn	Met	Leu	Ile	Ala	Leu	Met	Gly	Glu
705					710				715					720	
Thr	Val	Gly	Gln	Val	Ser	Lys	Glu	Ser	Lys	His	Ile	Trp	Lys	Leu	Gln
			725						730					735	
Trp	Ala	Thr	Thr	Ile	Leu	Asp	Ile	Glu	Arg	Ser	Phe	Pro	Val	Phe	Leu
		740						745					750		
Arg	Lys	Ala	Phe	Arg	Ser	Gly	Glu	Met	Val	Thr	Val	Gly	Lys	Ser	Ser
		755					760					765			
Asp	Gly	Thr	Pro	Asp	Arg	Arg	Trp	Cys	Phe	Arg	Val	Asp	Glu	Val	Asn
	770					775					780				
Trp	Ser	His	Trp	Asn	Gln	Asn	Leu	Gly	Ile	Ile	Asn	Glu	Asp	Pro	Gly
785					790				795					800	
Lys	Ser	Glu	Ile	Tyr	Gln	Tyr	Tyr	Gly	Phe	Ser	His	Thr	Val	Gly	Arg
			805					810						815	
Leu	Arg	Arg	Asp	Arg	Trp	Ser	Ser	Val	Val	Pro	Arg	Val	Val	Glu	Leu
			820					825					830		
Asn	Lys	Asn	Ser	Ser	Ala	Asp	Glu	Val	Val	Pro	Leu	Asp	Asn	Leu	
		835					840				845				
Gly	Asn	Pro	Asn	Cys	Asp	Gly	His	Gln	Gln	Gly	Tyr	Ala	Pro	Lys	Trp

850
Arg Thr Asp Asp Ala Pro Leu
865 870

860

<210> 15
<211> 2613
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (1)...(2613)

<223> Generic sequence that encompasses all nucleotide
sequences that encode mouse TRPV4 having amino
acid sequence as shown in SEQ ID NO:14

<221> misc_feature
<222> 69,78,102,105,138,141,144,150,165,264,279,282,318,354,402,
477,486,513,567,609,687,723,870,957,1062,1080,1116,1209,
1248,1251,1266,1269,1296,1323,1410,1431,1584,1626,1644,1671,1689,
1809,1890,1950,2001,2061,2064,2178,2187,2241,2274,2301,2304,2358,2406,
2433,2469,2472,2508,2511
<223> n = A,T,C or G if after TC;
n = T or C if after AG

<221> misc_feature
<222> 27,168,192,204,228,342,366,372,375,453,480,537,558,618,657,
672,696,711,744,747,807,813,945,948,960,1008,1065,1173,1176,1200,1212,
1338,1380,1392,1509,1530,1782,1848,1983,2238,2259,2271,2322,2325,2337,2448
,
2454,2457,2463,2484,2595
<223> n = A,T,C or G if after CG;
n = A or G if after AG

<221> misc_feature
<222> all "n" not specified above
<223> n = A,T,C or G

<400> 15
atg gcn gay ccn ggn gay ggn ccn mgn gcn gcn ccn ggn gar gtn gcn 48
Met Ala Asp Pro Gly Asp Gly Pro Arg Ala Ala Pro Gly Glu Val Ala
1 5 10 15

gar ccn ccn ggn gay gar wsn ggn acn wsn ggn ggn gar gcn tty ccn 96
Glu Pro Pro Gly Asp Glu Ser Gly Thr Ser Gly Gly Glu Ala Phe Pro
20 25 30

ytn wsn wsn ytn gcn aay ytn tty gar ggn gar gar ggn wsn wsn wsn 144
Leu Ser Ser Leu Ala Asn Leu Phe Glu Gly Glu Glu Gly Ser Ser Ser
35 40 45

ytn wsn ccn gtn gay gcn wsn mgn ccn gcn ggn ccn ggn gay ggn mgn 192
Leu Ser Pro Val Asp Ala Ser Arg Pro Ala Gly Pro Gly Asp Gly Arg
50 55 60

ccn aay ytn mgn atg aar tty car ggn gcn tty mgn aar ggn gtn ccn 240
Pro Asn Leu Arg Met Lys Phe Gln Gly Ala Phe Arg Lys Gly Val Pro
65 70 75 80

aay ccn ath gay ytn ytn gar wsn acn ytn tay gar wsn wsn gtn gtn 288
Asn Pro Ile Asp Leu Leu Glu Ser Thr Leu Tyr Glu Ser Ser Val Val
85 90 95

ccn ggn ccn aar aar gcn ccn atg gay wsn ytn tty gay tay ggn acn 336
Pro Gly Pro Lys Lys Ala Pro Met Asp Ser Leu Phe Asp Tyr Gly Thr
100 105 110

tay	mgn	cay	cay	ccn	wsn	gay	aay	aar	mgn	tgg	mgn	mgn	aar	gtn	gtn	384
Tyr	Arg	His	His	Pro	Ser	Asp	Asn	Lys	Arg	Trp	Arg	Arg	Lys	Val	Val	
		115					120					125				
gar	aar	car	ccn	car	wsn	ccn	aar	gcg	ccn	gcg	ccn	car	ccn	ccn	ccn	432
Glu	Lys	Gln	Pro	Gln	Ser	Pro	Lys	Ala	Pro	Ala	Pro	Gln	Pro	Pro	Pro	
	130					135					140					
ath	ytn	aar	gtn	tty	aay	mgn	ccn	ath	ytn	tty	gay	ath	gtn	wsn	mgn	480
Ile	Leu	Lys	Val	Phe	Asn	Arg	Pro	Ile	Leu	Phe	Asp	Ile	Val	Ser	Arg	
145					150					155					160	
ggn	wsn	acn	gcg	gay	ytn	gay	ggn	ytn	ytn	wsn	tty	ytn	ytn	acn	cay	528
Gly	Ser	Thr	Ala	Asp	Leu	Asp	Gly	Leu	Leu	Ser	Phe	Leu	Leu	Thr	His	
				165				170						175		
aar	aar	mgn	ytn	acn	gay	gar	gar	tty	mgn	gar	ccn	wsn	acn	ggn	aar	576
Lys	Lys	Arg	Leu	Thr	Asp	Glu	Glu	Phe	Arg	Glu	Pro	Ser	Thr	Gly	Lys	
			180					185					190			
acn	tgy	ytn	ccn	aar	gcg	ytn	ytn	aay	ytn	wsn	aay	ggn	mgn	aay	gay	624
Thr	Cys	Leu	Pro	Lys	Ala	Leu	Leu	Asn	Leu	Ser	Asn	Gly	Arg	Asn	Asp	
		195					200					205				
acn	ath	ccn	gtn	ytn	ytn	gay	ath	gcg	gar	mgn	acn	ggn	aay	atg	mgn	672
Thr	Ile	Pro	Val	Leu	Leu	Asp	Ile	Ala	Glu	Arg	Thr	Gly	Asn	Met	Arg	
	210					215					220					
gar	tty	ath	aay	wsn	ccn	tty	mgn	gay	ath	tay	tay	mgn	ggn	car	acn	720
Glu	Phe	Ile	Asn	Ser	Pro	Phe	Arg	Asp	Ile	Tyr	Tyr	Arg	Gly	Gln	Thr	
225					230					235					240	
wsn	ytn	cay	ath	gcg	ath	gar	mgn	mgn	tgy	aar	cay	tay	gtn	gar	ytn	768
Ser	Leu	His	Ile	Ala	Ile	Glu	Arg	Arg	Cys	Lys	His	Tyr	Val	Glu	Leu	
				245					250					255		
ytn	gtn	gcg	car	ggn	gcg	gay	gtn	cay	gcg	car	gcg	mgn	ggn	mgn	tty	816
Leu	Val	Ala	Gln	Gly	Ala	Asp	Val	His	Ala	Gln	Ala	Arg	Gly	Arg	Phe	
			260					265					270			
tty	car	ccn	aar	gay	gar	ggn	ggn	tay	tty	tay	tty	ggn	gar	ytn	ccn	864
Phe	Gln	Pro	Lys	Asp	Glu	Gly	Gly	Tyr	Phe	Tyr	Phe	Gly	Glu	Leu	Pro	
		275					280					285				
ytn	wsn	ytn	gcg	gcg	tgy	acn	aay	car	ccn	cay	ath	gtn	aay	tay	ytn	912
Leu	Ser	Leu	Ala	Ala	Cys	Thr	Asn	Gln	Pro	His	Ile	Val	Asn	Tyr	Leu	
	290					295					300					
acn	gar	aay	ccn	cay	aar	aar	gcg	gay	atg	mgn	mgn	car	gay	wsn	mgn	960
Thr	Glu	Asn	Pro	His	Lys	Lys	Ala	Asp	Met	Arg	Arg	Gln	Asp	Ser	Arg	
305					310					315					320	
ggn	aay	acn	gtn	ytn	cay	gcg	ytn	gtn	gcg	ath	gcg	gay	aay	acn	mgn	1008
Gly	Asn	Thr	Val	Leu	His	Ala	Leu	Val	Ala	Ile	Ala	Asp	Asn	Thr	Arg	
				325					330					335		
gar	aay	acn	aar	tty	gtn	acn	aar	atg	tay	gay	ytn	ytn	ytn	ytn	aar	1056
Glu	Asn	Thr	Lys	Phe	Val	Thr	Lys	Met	Tyr	Asp	Leu	Leu	Leu	Leu	Lys	
			340					345					350			
tgy	wsn	mgn	ytn	tty	ytn	gay	wsn	aay	ytn	gar	acn	gtn	ytn	aay	aay	1104
Cys	Ser	Arg	Leu	Phe	Leu	Asp	Ser	Asn	Leu	Glu	Thr	Val	Leu	Asn	Asn	
		355					360					365				
gay	ggn	ytn	wsn	ccn	ytn	atg	atg	gcg	gcg	aar	acn	ggn	aar	ath	ggn	1152
Asp	Gly	Leu	Ser	Pro	Leu	Met	Met	Ala	Ala	Lys	Thr	Gly	Lys	Ile	Gly	
		370				375					380					

gtn	tty	car	cay	ath	ath	mgn	mgn	gar	gtn	acn	gay	gar	gay	acn	mgn	1200
Val	Phe	Gln	His	Ile	Ile	Arg	Arg	Glu	Val	Thr	Asp	Glu	Asp	Thr	Arg	
385					390					395					400	
cay	ytn	wsn	mgn	aar	tty	aar	gay	tgg	gcn	tay	ggn	ccn	gtn	tay	wsn	1248
His	Leu	Ser	Arg	Lys	Phe	Lys	Asp	Trp	Ala	Tyr	Gly	Pro	Val	Tyr	Ser	
				405					410					415		
wsn	ytn	tay	gay	ytn	wsn	wsn	ytn	gay	acn	tgy	ggn	gar	gar	gtn	wsn	1296
Ser	Leu	Tyr	Asp	Leu	Ser	Ser	Leu	Asp	Thr	Cys	Gly	Glu	Glu	Val	Ser	
			420					425					430			
gtn	ytn	gar	ath	ytn	gtn	tay	aay	wsn	aar	ath	gar	aay	mgn	cay	gar	1344
Val	Leu	Glu	Ile	Leu	Val	Tyr	Asn	Ser	Lys	Ile	Glu	Asn	Arg	His	Glu	
		435					440					445				
atg	ytn	gcn	gtn	gar	ccn	ath	aay	gar	ytn	ytn	mgn	gay	aar	tgg	mgn	1392
Met	Leu	Ala	Val	Glu	Pro	Ile	Asn	Glu	Leu	Leu	Arg	Asp	Lys	Trp	Arg	
		450				455					460					
aar	tty	ggn	gcn	gtn	wsn	tty	tay	ath	aay	gtn	gtn	wsn	tay	ytn	tgy	1440
Lys	Phe	Gly	Ala	Val	Ser	Phe	Tyr	Ile	Asn	Val	Val	Ser	Tyr	Leu	Cys	
465					470					475					480	
gcn	atg	gtn	ath	tty	acn	ytn	acn	gcn	tay	tay	car	ccn	ytn	gar	ggn	1488
Ala	Met	Val	Ile	Phe	Thr	Leu	Thr	Ala	Tyr	Tyr	Gln	Pro	Leu	Gar	Gly	
			485						490					495		
acn	ccn	ccn	tay	ccn	tay	mgn	acn	acn	gtn	gay	tay	ytn	mgn	ytn	gcn	1536
Thr	Pro	Pro	Tyr	Pro	Tyr	Arg	Thr	Thr	Val	Asp	Tyr	Leu	Arg	Leu	Ala	
			500					505					510			
ggn	gar	gtn	ath	acn	ytn	tty	acn	ggn	gtn	ytn	tty	tty	tty	acn	wsn	1584
Gly	Glu	Val	Ile	Thr	Leu	Phe	Thr	Gly	Val	Leu	Phe	Phe	Phe	Thr	Ser	
		515					520					525				
ath	aar	gay	ytn	tty	acn	aar	aar	tgy	ccn	ggn	gtn	aay	wsn	ytn	tty	1632
Ile	Lys	Asp	Leu	Phe	Thr	Lys	Lys	Cys	Pro	Gly	Val	Asn	Ser	Leu	Phe	
		530				535					540					
gtn	gay	ggn	wsn	tty	car	ytn	ytn	tay	tty	ath	tay	wsn	gtn	ytn	gtn	1680
Val	Asp	Gly	Ser	Phe	Gln	Leu	Leu	Tyr	Phe	Ile	Tyr	Ser	Val	Leu	Val	
545					550					555					560	
gtn	gtn	wsn	gcn	gcn	ytn	tay	ytn	gcn	ggn	ath	gar	gcn	tay	ytn	gcn	1728
Val	Val	Ser	Ala	Ala	Leu	Tyr	Leu	Ala	Gly	Ile	Glu	Ala	Tyr	Leu	Ala	
			565						570					575		
gtn	atg	gtn	tty	gcn	ytn	gtn	ytn	ggn	tgg	atg	aay	gcn	ytn	tay	tty	1776
Val	Met	Val	Phe	Ala	Leu	Val	Leu	Gly	Trp	Met	Asn	Ala	Leu	Tyr	Phe	
			580					585					590			
acn	mgn	ggn	ytn	aar	ytn	acn	ggn	acn	tay	wsn	ath	atg	ath	car	aar	1824
Thr	Arg	Gly	Leu	Lys	Leu	Thr	Gly	Thr	Tyr	Ser	Ile	Met	Ile	Gln	Lys	
		595					600					605				
ath	ytn	tty	aar	gay	ytn	tty	mgn	tty	ytn	ytn	gtn	tay	ytn	ytn	tty	1872
Ile	Leu	Phe	Lys	Asp	Leu	Phe	Arg	Phe	Leu	Leu	Val	Tyr	Leu	Leu	Phe	
		610				615					620					
atg	ath	ggn	tay	gcn	wsn	gcn	ytn	gtn	acn	ytn	ytn	aay	ccn	tgy	acn	1920
Met	Ile	Gly	Tyr	Ala	Ser	Ala	Leu	Val	Thr	Leu	Leu	Asn	Pro	Cys	Thr	
625					630					635					640	
aay	atg	aar	gtn	tgy	gay	gar	gay	car	wsn	aay	tgy	acn	gtn	ccn	acn	1968
Asn	Met	Lys	Val	Cys	Asp	Glu	Asp	Gln	Ser	Asn	Cys	Thr	Val	Pro	Thr	
			645						650					655		

tay ccn gcN tgy mgn gay wsn gar acn tty wsn gcN tty ytn ytn gay	2016
Tyr Pro Ala Cys Arg Asp Ser Glu Thr Phe Ser Ala Phe Leu Leu Asp	
660 665 670	
ytn tty aar ytn acn ath ggn atg ggn gay ytn gar atg ytn wsn wsn	2064
Leu Phe Lys Leu Thr Ile Gly Met Gly Asp Leu Glu Met Leu Ser Ser	
675 680 685	
gcN aar tay ccn gtn gtn tty ath ytn ytn ytn gtn acn tay ath ath	2112
Ala Lys Tyr Pro Val Val Phe Ile Leu Leu Leu Val Thr Tyr Ile Ile	
690 695 700	
ytn acn tty gtn ytn ytn ytn aay atg ytn ath gcN ytn atg ggn gar	2160
Leu Thr Phe Val Leu Leu Asn Met Leu Ile Ala Leu Met Gly Glu	
705 710 715 720	
acn gtn ggn car gtn wsn aar gar wsn aar cay ath tgg aar ytn car	2208
Thr Val Gly Gln Val Ser Lys Glu Ser Lys His Ile Trp Lys Leu Gln	
725 730 735	
tgg gcN acn acn ath ytn gay ath gar mgn wsn tty ccn gtn tty ytn	2256
Trp Ala Thr Thr Ile Leu Asp Ile Glu Arg Ser Phe Pro Val Phe Leu	
740 745 750	
mgn aar gcN tty mgn wsn ggn gar atg gtn acn gtn ggn aar wsn wsn	2304
Arg Lys Ala Phe Arg Ser Gly Glu Met Val Thr Val Gly Lys Ser Ser	
755 760 765	
gay ggn acn ccn gay mgn mgn tgg tgy tty mgn gtn gay gar gtn aay	2352
Asp Gly Thr Pro Asp Arg Arg Trp Cys Phe Arg Val Asp Glu Val Asn	
770 775 780	
tgg wsn cay tgg aay car aay ytn ggn ath ath aay gar gay ccn ggn	2400
Trp Ser His Trp Asn Gln Asn Leu Gly Ile Ile Asn Glu Asp Pro Gly	
785 790 795 800	
aar wsn gar ath tay car tay tay ggn tty wsn cay acn gtn ggn mgn	2448
Lys Ser Glu Ile Tyr Gln Tyr Tyr Gly Phe Ser His Thr Val Gly Arg	
805 810 815	
ytn mgn mgn gay mgn tgg wsn wsn gtn gtn ccn mgn gtn gtn gar ytn	2496
Leu Arg Arg Asp Arg Trp Ser Ser Val Val Pro Arg Val Val Glu Leu	
820 825 830	
aay aar aay wsn wsn gcN gay gar gtn gtn gtn ccn ytn gay aay ytn	2544
Asn Lys Asn Ser Ser Ala Asp Glu Val Val Val Pro Leu Asp Asn Leu	
835 840 845	
ggn aay ccn aay tgy gay ggn cay car car ggn tay gcN ccn aar tgg	2592
Gly Asn Pro Asn Cys Asp Gly His Gln Gln Gly Tyr Ala Pro Lys Trp	
850 855 860	
mgn acn gay gay gcN ccn ytn	2613
Arg Thr Asp Asp Ala Pro Leu	
865 870	

<210> 16
 <211> 2616
 <212> DNA
 <213> Homo sapiens

 <220>
 <221> CDS
 <222> (1) ... (2616)

 <400> 16

atg gcg gat tcc agc gaa ggc ccc cgc gcg ggg ccc ggg gag gtg gct	48
Met Ala Asp Ser Ser Glu Gly Pro Arg Ala Gly Pro Gly Glu Val Ala	
1 5 10 15	
gag ctc ccc ggg gat gag agt ggc acc cca ggt ggg gag gct ttt cct	96
Glu Leu Pro Gly Asp Glu Ser Gly Thr Pro Gly Gly Glu Ala Phe Pro	
20 25 30	
ctc tcc tcc ctg gcc aat ctg ttt gag ggg gag gat ggc tcc ctt tcg	144
Leu Ser Ser Leu Ala Asn Leu Phe Glu Gly Glu Asp Gly Ser Leu Ser	
35 40 45	
ccc tca ccg gct gat gcc agt cgc cct gct ggc cca ggc gat ggg cga	192
Pro Ser Pro Ala Asp Ala Ser Arg Pro Ala Gly Pro Gly Asp Gly Arg	
50 55 60	
cca aat ctg cgc atg aag ttc cag ggc gcc ttc cgc aag ggg gtg ccc	240
Pro Asn Leu Arg Met Lys Phe Gln Gly Ala Phe Arg Lys Gly Val Pro	
65 70 75 80	
aac ccc atc gat ctg ctg gag tcc acc cta tat gag tcc tcg gtg gtg	288
Asn Pro Ile Asp Leu Leu Glu Ser Thr Leu Tyr Glu Ser Ser Val Val	
85 90 95	
cct ggg ccc aag aaa gca ccc atg gac tca ctg ttt gac tac ggc acc	336
Pro Gly Pro Lys Lys Ala Pro Met Asp Ser Leu Phe Asp Tyr Gly Thr	
100 105 110	
tat cgt cac cac tcc agt gac aac aag agg tgg agg aag aag atc ata	384
Tyr Arg His His Ser Ser Asp Asn Lys Arg Trp Arg Lys Lys Ile Ile	
115 120 125	
gag aag cag ccg cag agc ccc aaa gcc cct gcc cct cag ccg ccc ccc	432
Glu Lys Gln Pro Gln Ser Pro Lys Ala Pro Ala Pro Gln Pro Pro Pro	
130 135 140	
atc ctc aaa gtc ttc aac cgg cct atc ctc ttt gac atc gtg tcc cgg	480
Ile Leu Lys Val Phe Asn Arg Pro Ile Leu Phe Asp Ile Val Ser Arg	
145 150 155 160	
ggc tcc act gct gac ctg gac ggg ctg ctc cca ttc ttg ctg acc cac	528
Gly Ser Thr Ala Asp Leu Asp Gly Leu Leu Pro Phe Leu Leu Thr His	
165 170 175	
aag aaa cgc cta act gat gag gag ttt cga gag cca tct acg ggg aag	576
Lys Lys Arg Leu Thr Asp Glu Glu Phe Arg Glu Pro Ser Thr Gly Lys	
180 185 190	
acc tgc ctg ccc aag gcc ttg ctg aac ctg agc aat ggc cgc aac gac	624
Thr Cys Leu Pro Lys Ala Leu Leu Asn Leu Ser Asn Gly Arg Asn Asp	
195 200 205	
acc atc cct gtg ctg ctg gac atc gcg gag cgc acc ggc aac atg cgg	672
Thr Ile Pro Val Leu Leu Asp Ile Ala Glu Arg Thr Gly Asn Met Arg	
210 215 220	
gag ttc att aac tcg ccc ttc cgt gac atc tac tat cga ggt cag aca	720
Glu Phe Ile Asn Ser Pro Phe Arg Asp Ile Tyr Tyr Arg Gly Gln Thr	
225 230 235 240	
gcc ctg cac atc gcc att gag cgt cgc tgc aaa cac tac gtg gaa ctt	768
Ala Leu His Ile Ala Ile Glu Arg Arg Cys Lys His Tyr Val Glu Leu	
245 250 255	
ctc gtg gcc cag gga gct gat gtc cac gcc cag gcc cgt ggg cgc ttc	816
Leu Val Ala Gln Gly Ala Asp Val His Ala Gln Ala Arg Gly Arg Phe	
260 265 270	

52/75

ttc	cag	ccc	aag	gat	gag	ggg	ggc	tac	ttc	tac	ttt	ggg	gag	ctg	ccc	864
Phe	Gln	Pro	Lys	Asp	Glu	Gly	Gly	Tyr	Phe	Tyr	Phe	Gly	Glu	Leu	Pro	
		275					280					285				
ctg	tcg	ctg	gct	gcc	tgc	acc	aac	cag	ccc	cac	att	gtc	aac	tac	ctg	912
Leu	Ser	Leu	Ala	Ala	Cys	Thr	Asn	Gln	Pro	His	Ile	Val	Asn	Tyr	Leu	
		290				295					300					
acg	gag	aac	ccc	cac	aag	aag	gcg	gac	atg	cgg	cgc	cag	gac	tcg	cga	960
Thr	Glu	Asn	Pro	His	Lys	Lys	Ala	Asp	Met	Arg	Arg	Gln	Asp	Ser	Arg	
305					310					315					320	
ggc	aac	aca	gtg	ctg	cat	gcg	ctg	gtg	gcc	att	gct	gac	aac	acc	cgt	1008
Gly	Asn	Thr	Val	Leu	His	Ala	Leu	Val	Ala	Ile	Ala	Asp	Asn	Thr	Arg	
			325					330						335		
gag	aac	acc	aag	ttt	gtt	acc	aag	atg	tac	gac	ctg	ctg	ctg	ctc	aag	1056
Glu	Asn	Thr	Lys	Phe	Val	Thr	Lys	Met	Tyr	Asp	Leu	Leu	Leu	Leu	Lys	
			340					345					350			
tgt	gcc	cgc	ctc	ttc	ccc	gac	agc	aac	ctg	gag	gcc	gtg	ctc	aac	aac	1104
Cys	Ala	Arg	Leu	Phe	Pro	Asp	Ser	Asn	Leu	Glu	Ala	Val	Leu	Asn	Asn	
		355				360						365				
gac	ggc	ctc	tcg	ccc	ctc	atg	atg	gct	gcc	aag	acg	ggc	aag	att	ggg	1152
Asp	Gly	Leu	Ser	Pro	Leu	Met	Met	Ala	Ala	Lys	Thr	Gly	Lys	Ile	Gly	
	370					375					380					
atc	ttt	cag	cac	atc	atc	cgg	cgg	gag	gtg	acg	gat	gag	gac	aca	cgg	1200
Ile	Phe	Gln	His	Ile	Ile	Arg	Arg	Glu	Val	Thr	Asp	Glu	Asp	Thr	Arg	
					390					395					400	
cac	ctg	tcc	cgc	aag	ttc	aag	gac	tgg	gcc	tat	ggg	cca	gtg	tat	tcc	1248
His	Leu	Ser	Arg	Lys	Phe	Lys	Asp	Trp	Ala	Tyr	Gly	Pro	Val	Tyr	Ser	
				405					410					415		
tcg	ctt	tat	gac	ctc	tcc	tcc	ctg	gac	acg	tgt	ggg	gaa	gag	gcc	tcc	1296
Ser	Leu	Tyr	Asp	Leu	Ser	Ser	Leu	Asp	Thr	Cys	Gly	Glu	Glu	Ala	Ser	
			420					425					430			
gtg	ctg	gag	atc	ctg	gtg	tac	aac	agc	aag	att	gag	aac	cgc	cac	gag	1344
Val	Leu	Glu	Ile	Leu	Val	Tyr	Asn	Ser	Lys	Ile	Glu	Asn	Arg	His	Glu	
		435					440					445				
atg	ctg	gct	gtg	gag	ccc	atc	aat	gaa	ctg	ctg	cgg	gac	aag	tgg	cgc	1392
Met	Leu	Ala	Val	Glu	Pro	Ile	Asn	Glu	Leu	Leu	Arg	Asp	Lys	Trp	Arg	
		450				455					460					
aag	ttc	ggg	gcc	gtc	tcc	ttc	tac	atc	aac	gtg	gtc	tcc	tac	ctg	tgt	1440
Lys	Phe	Gly	Ala	Val	Ser	Phe	Tyr	Ile	Asn	Val	Val	Ser	Tyr	Leu	Cys	
		465			470					475					480	
gcc	atg	gtc	atc	ttc	act	ctc	acc	gcc	tac	tac	cag	ccg	ctg	gag	ggc	1488
Ala	Met	Val	Ile	Phe	Thr	Leu	Thr	Ala	Tyr	Tyr	Gln	Pro	Leu	Glu	Gly	
				485					490					495		
aca	ccg	ccg	tac	cct	tac	cgc	acc	acg	gtg	gac	tac	ctg	cgg	ctg	gct	1536
Thr	Pro	Pro	Tyr	Pro	Tyr	Arg	Thr	Thr	Val	Asp	Tyr	Leu	Arg	Leu	Ala	
			500					505					510			
ggc	gag	gtc	att	acg	ctc	ttc	act	ggg	gtc	ctg	ttc	ttc	ttc	acc	aac	1584
Gly	Glu	Val	Ile	Thr	Leu	Phe	Thr	Gly	Val	Leu	Phe	Phe	Phe	Thr	Asn	
		515					520					525				
atc	aaa	gac	ttg	ttc	atg	aag	aaa	tgc	cct	gga	gtg	aat	tct	ctc	ttc	1632
Ile	Lys	Asp	Leu	Phe	Met	Lys	Lys	Cys	Pro	Gly	Val	Asn	Ser	Leu	Phe	
		530				535					540					

53/75

att gat ggc tcc ttc cag ctg ctc tac ttc atc tac tct gtc ctg gtg	1680
Ile Asp Gly Ser Phe Gln Leu Leu Tyr Phe Ile Tyr Ser Val Leu Val	
545 550 555 560	
atc gtc tca gca gcc ctc tac ctg gca ggg atc gag gcc tac ctg gcc	1728
Ile Val Ser Ala Ala Leu Tyr Leu Ala Gly Ile Glu Ala Tyr Leu Ala	
565 570 575	
gtg atg gtc ttt gcc ctg gtc ctg ggc tgg atg aat gcc ctt tac ttc	1776
Val Met Val Phe Ala Leu Val Leu Gly Trp Met Asn Ala Leu Tyr Phe	
580 585 590	
acc cgt ggg ctg aag ctg acg ggg acc tat agc atc atg atc cag aag	1824
Thr Arg Gly Leu Lys Leu Thr Gly Thr Tyr Ser Ile Met Ile Gln Lys	
595 600 605	
att ctc ttc aag gac ctt ttc cga ttc ctg ctc gtc tac ttg ctc ttc	1872
Ile Leu Phe Lys Asp Leu Phe Arg Phe Leu Leu Val Tyr Leu Leu Phe	
610 615 620	
atg atc ggc tac gct tca gcc ctg gtc tcc ctc ctg aac ccg tgt gcc	1920
Met Ile Gly Tyr Ala Ser Ala Leu Val Ser Leu Leu Asn Pro Cys Ala	
625 630 635 640	
aac atg aag gtg tgc aat gag gac cag acc aac tgc aca gtg ccc act	1968
Asn Met Lys Val Cys Asn Glu Asp Gln Thr Asn Cys Thr Val Pro Thr	
645 650 655	
tac ccc tcg tgc cgt gac agc gag acc ttc agc acc ttc ctc ctg gac	2016
Tyr Pro Ser Cys Arg Asp Ser Glu Thr Phe Ser Thr Phe Leu Leu Asp	
660 665 670	
ctg ttt aag ctg acc atc gcc atg gcc gac ctg gag atg ctg agc agc	2064
Leu Phe Lys Leu Thr Ile Gly Met Gly Asp Leu Glu Met Leu Ser Ser	
675 680 685	
acc aag tac ccc gtg gtc ttc atc atc ctg ctg gtg acc tac atc atc	2112
Thr Lys Tyr Pro Val Val Phe Ile Ile Leu Leu Val Thr Tyr Ile Ile	
690 695 700	
ctc acc ttt gtg ctg ctc ctc aac atg ctc att gcc ctc atg ggc gag	2160
Leu Thr Phe Val Leu Leu Leu Asn Met Leu Ile Ala Leu Met Gly Glu	
705 710 715 720	
aca gtg ggc cag gtc tcc aag gag agc aag cac atc tgg aag ctg cag	2208
Thr Val Gly Gln Val Ser Lys Glu Ser Lys His Ile Trp Lys Leu Gln	
725 730 735	
tgg gcc acc acc atc ctg gac att gag cgc tcc ttc ccc gta ttc ctg	2256
Trp Ala Thr Ile Leu Asp Ile Glu Arg Ser Phe Pro Val Phe Leu	
740 745 750	
agg aag gcc ttc cgc tct ggg gag atg gtc acc gtg ggc aag agc tcg	2304
Arg Lys Ala Phe Arg Ser Gly Glu Met Val Thr Val Gly Lys Ser Ser	
755 760 765	
gac ggc act cct gac cgc agg tgg tgc ttc agg gtg gat gag gtg aac	2352
Asp Gly Thr Pro Asp Arg Arg Trp Cys Phe Arg Val Asp Glu Val Asn	
770 775 780	
tgg tct cac tgg aac cag aac ttg ggc atc atc aac gag gac ccg ggc	2400
Trp Ser His Trp Asn Gln Asn Leu Gly Ile Ile Asn Glu Asp Pro Gly	
785 790 795 800	
aag aat gag acc tac cag tat tat ggc ttc tcg cat acc gtg ggc cgc	2448
Lys Asn Glu Thr Tyr Gln Tyr Tyr Gly Phe Ser His Thr Val Gly Arg	
805 810 815	

54/75

ctc	cgc	agg	gat	cgc	tgg	tcc	tcg	gtg	gta	ccc	cgc	gtg	gtg	gaa	ctg	2496
Leu	Arg	Arg	Asp	Arg	Trp	Ser	Ser	Val	Val	Pro	Arg	Val	Val	Glu	Leu	
			820					825					830			
aac	aag	aac	tcg	aac	ccg	gac	gag	gtg	gtg	gtg	cct	ctg	gac	agc	atg	2544
Asn	Lys	Asn	Ser	Asn	Pro	Asp	Glu	Val	Val	Val	Pro	Leu	Asp	Ser	Met	
		835					840					845				
ggg	aac	ccc	cgc	tgc	gat	ggc	cac	cag	cag	ggt	tac	ccc	cgc	aag	tgg	2592
Gly	Asn	Pro	Arg	Cys	Asp	Gly	His	Gln	Gln	Gly	Tyr	Pro	Arg	Lys	Trp	
	850					855					860					
agg	act	gag	gac	gcc	ccg	ctc	tag									2616
Arg	Thr	Glu	Asp	Ala	Pro	Leu	*									
865					870											

<210> 17

<211> 871

<212> PRT

<213> Homo sapiens

<400> 17

Met	Ala	Asp	Ser	Ser	Glu	Gly	Pro	Arg	Ala	Gly	Pro	Gly	Glu	Val	Ala	
1				5					10					15		
Glu	Leu	Pro	Gly	Asp	Glu	Ser	Gly	Thr	Pro	Gly	Gly	Glu	Ala	Phe	Pro	
			20					25					30			
Leu	Ser	Ser	Leu	Ala	Asn	Leu	Phe	Glu	Gly	Glu	Asp	Gly	Ser	Leu	Ser	
		35					40					45				
Pro	Ser	Pro	Ala	Asp	Ala	Ser	Arg	Pro	Ala	Gly	Pro	Gly	Asp	Gly	Arg	
	50					55					60					
Pro	Asn	Leu	Arg	Met	Lys	Phe	Gln	Gly	Ala	Phe	Arg	Lys	Gly	Val	Pro	
	65				70					75					80	
Asn	Pro	Ile	Asp	Leu	Leu	Glu	Ser	Thr	Leu	Tyr	Glu	Ser	Ser	Val	Val	
				85					90					95		
Pro	Gly	Pro	Lys	Lys	Ala	Pro	Met	Asp	Ser	Leu	Phe	Asp	Tyr	Gly	Thr	
			100					105					110			
Tyr	Arg	His	His	Ser	Ser	Asp	Asn	Lys	Arg	Trp	Arg	Lys	Lys	Ile	Ile	
		115					120					125				
Glu	Lys	Gln	Pro	Gln	Ser	Pro	Lys	Ala	Pro	Ala	Pro	Gln	Pro	Pro	Pro	
	130					135					140					
Ile	Leu	Lys	Val	Phe	Asn	Arg	Pro	Ile	Leu	Phe	Asp	Ile	Val	Ser	Arg	
	145				150					155					160	
Gly	Ser	Thr	Ala	Asp	Leu	Asp	Gly	Leu	Leu	Pro	Phe	Leu	Leu	Thr	His	
				165				170						175		
Lys	Lys	Arg	Leu	Thr	Asp	Glu	Glu	Phe	Arg	Glu	Pro	Ser	Thr	Gly	Lys	
			180					185					190			
Thr	Cys	Leu	Pro	Lys	Ala	Leu	Leu	Asn	Leu	Ser	Asn	Gly	Arg	Asn	Asp	
		195				200						205				
Thr	Ile	Pro	Val	Leu	Leu	Asp	Ile	Ala	Glu	Arg	Thr	Gly	Asn	Met	Arg	
	210					215					220					
Glu	Phe	Ile	Asn	Ser	Pro	Phe	Arg	Asp	Ile	Tyr	Tyr	Arg	Gly	Gln	Thr	
	225				230					235					240	
Ala	Leu	His	Ile	Ala	Ile	Glu	Arg	Arg	Cys	Lys	His	Tyr	Val	Glu	Leu	
				245					250					255		
Leu	Val	Ala	Gln	Gly	Ala	Asp	Val	His	Ala	Gln	Ala	Arg	Gly	Arg	Phe	
			260					265					270			
Phe	Gln	Pro	Lys	Asp	Glu	Gly	Gly	Tyr	Phe	Tyr	Phe	Gly	Glu	Leu	Pro	
		275					280					285				
Leu	Ser	Leu	Ala	Ala	Cys	Thr	Asn	Gln	Pro	His	Ile	Val	Asn	Tyr	Leu	
		290				295					300					
Thr	Glu	Asn	Pro	His	Lys	Lys	Ala	Asp	Met	Arg	Arg	Gln	Asp	Ser	Arg	
	305				310					315					320	
Gly	Asn	Thr	Val	Leu	His	Ala	Leu	Val	Ala	Ile	Ala	Asp	Asn	Thr	Arg	
				325					330					335		
Glu	Asn	Thr	Lys	Phe	Val	Thr	Lys	Met	Tyr	Asp	Leu	Leu	Leu	Leu	Lys	
			340					345					350			
Cys	Ala	Arg	Leu	Phe	Pro	Asp	Ser	Asn	Leu	Glu	Ala	Val	Leu	Asn	Asn	

355	360	365
Asp Gly Leu Ser Pro Leu Met Met Ala Ala Lys Thr Gly Lys Ile Gly		
370	375	380
Ile Phe Gln His Ile Ile Arg Arg Glu Val Thr Asp Glu Asp Thr Arg		
385	390	395
His Leu Ser Arg Lys Phe Lys Asp Trp Ala Tyr Gly Pro Val Tyr Ser		
405	410	415
Ser Leu Tyr Asp Leu Ser Ser Leu Asp Thr Cys Gly Glu Glu Ala Ser		
420	425	430
Val Leu Glu Ile Leu Val Tyr Asn Ser Lys Ile Glu Asn Arg His Glu		
435	440	445
Met Leu Ala Val Glu Pro Ile Asn Glu Leu Leu Arg Asp Lys Trp Arg		
450	455	460
Lys Phe Gly Ala Val Ser Phe Tyr Ile Asn Val Val Ser Tyr Leu Cys		
465	470	475
Ala Met Val Ile Phe Thr Leu Thr Ala Tyr Tyr Gln Pro Leu Glu Gly		
485	490	495
Thr Pro Pro Tyr Pro Tyr Arg Thr Thr Val Asp Tyr Leu Arg Leu Ala		
500	505	510
Gly Glu Val Ile Thr Leu Phe Thr Gly Val Leu Phe Phe Phe Thr Asn		
515	520	525
Ile Lys Asp Leu Phe Met Lys Lys Cys Pro Gly Val Asn Ser Leu Phe		
530	535	540
Ile Asp Gly Ser Phe Gln Leu Leu Tyr Phe Ile Tyr Ser Val Leu Val		
545	550	555
Ile Val Ser Ala Ala Leu Tyr Leu Ala Gly Ile Glu Ala Tyr Leu Ala		
565	570	575
Val Met Val Phe Ala Leu Val Leu Gly Trp Met Asn Ala Leu Tyr Phe		
580	585	590
Thr Arg Gly Leu Lys Leu Thr Gly Thr Tyr Ser Ile Met Ile Gln Lys		
595	600	605
Ile Leu Phe Lys Asp Leu Phe Arg Phe Leu Leu Val Tyr Leu Leu Phe		
610	615	620
Met Ile Gly Tyr Ala Ser Ala Leu Val Ser Leu Leu Asn Pro Cys Ala		
625	630	635
Asn Met Lys Val Cys Asn Glu Asp Gln Thr Asn Cys Thr Val Pro Thr		
645	650	655
Tyr Pro Ser Cys Arg Asp Ser Glu Thr Phe Ser Thr Phe Leu Leu Asp		
660	665	670
Leu Phe Lys Leu Thr Ile Gly Met Gly Asp Leu Glu Met Leu Ser Ser		
675	680	685
Thr Lys Tyr Pro Val Val Phe Ile Ile Leu Leu Val Thr Tyr Ile Ile		
690	695	700
Leu Thr Phe Val Leu Leu Leu Asn Met Leu Ile Ala Leu Met Gly Glu		
705	710	715
Thr Val Gly Gln Val Ser Lys Glu Ser Lys His Ile Trp Lys Leu Gln		
725	730	735
Trp Ala Thr Thr Ile Leu Asp Ile Glu Arg Ser Phe Pro Val Phe Leu		
740	745	750
Arg Lys Ala Phe Arg Ser Gly Glu Met Val Thr Val Gly Lys Ser Ser		
755	760	765
Asp Gly Thr Pro Asp Arg Arg Trp Cys Phe Arg Val Asp Glu Val Asn		
770	775	780
Trp Ser His Trp Asn Gln Asn Leu Gly Ile Ile Asn Glu Asp Pro Gly		
785	790	795
Lys Asn Glu Thr Tyr Gln Tyr Tyr Gly Phe Ser His Thr Val Gly Arg		
805	810	815
Leu Arg Arg Asp Arg Trp Ser Ser Val Val Pro Arg Val Val Glu Leu		
820	825	830
Asn Lys Asn Ser Asn Pro Asp Glu Val Val Val Pro Leu Asp Ser Met		
835	840	845
Gly Asn Pro Arg Cys Asp Gly His Gln Gln Gly Tyr Pro Arg Lys Trp		
850	855	860
Arg Thr Glu Asp Ala Pro Leu		
865	870	

<210> 18

<211> 2613
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> CDS
 <222> (1)...(2613)

<223> Generic sequence that encompasses all nucleotide sequences that encode human TRPV4 having amino acid sequence as shown in SEQ ID NO:17

<221> misc feature
 <222> 12,15,69,102,105,138,144,150,165,264,279,282,318,351,354,402,477,486,567,609,687,870,957,1080,1116,1209,1248,1251,1266,1269,1296,1323,1410,1431,1626,1644,1671,1689,1809,1890,1902,1977,1989,2001,2061,2064,2178,2187,2241,2274,2301,2304,2358,2433,2469,2472,2508,2541
 <223> n = A,T,C or G if after TC;
 n = T or C if after AG

<221> misc feature
 <222> 27,168,192,204,228,342,366,372,453,480,537,558,618,657,672,696,711,744,747,807,813,945,948,960,1008,1065,1173,1176,1200,1212,1338,1380,1392,1509,1530,1782,1848,1983,2238,2259,2271,2322,2325,2337,2448,2454,2457,2463,2484,2556,2586,2595
 <223> n = A,T,C or G if after CG;
 n = A or G if after AG

<221> misc feature
 <222> all "n" not specified above
 <223> n = A,T,C or G

<400> 18
 atg gcn gay wsn wsn gar ggn ccn mgn gcn ggn ccn ggn gar gtn gcn 48
 Met Ala Asp Ser Ser Glu Gly Pro Arg Ala Gly Pro Gly Glu Val Ala
 1 5 10 15
 gar ytn ccn ggn gay gar wsn ggn acn ccn ggn ggn gar gcn tty ccn 96
 Glu Leu Pro Gly Asp Glu Ser Gly Thr Pro Gly Gly Glu Ala Phe Pro
 20 25 30
 ytn wsn wsn ytn gcn aay ytn tty gar ggn gar gay ggn wsn ytn wsn 144
 Leu Ser Ser Leu Ala Asn Leu Phe Glu Gly Glu Asp Gly Ser Leu Ser
 35 40 45
 ccn wsn ccn gcn gay gcn wsn mgn ccn gcn ggn ccn ggn gay ggn mgn 192
 Pro Ser Pro Ala Asp Ala Ser Arg Pro Ala Gly Pro Gly Asp Gly Arg
 50 55 60
 ccn aay ytn mgn atg aar tty car ggn gcn tty mgn aar ggn gtn ccn 240
 Pro Asn Leu Arg Met Lys Phe Gln Gly Ala Phe Arg Lys Gly Val Pro
 65 70 75 80
 aay ccn ath gay ytn ytn gar wsn acn ytn tay gar wsn wsn gtn gtn 288
 Asn Pro Ile Asp Leu Leu Glu Ser Thr Leu Tyr Glu Ser Ser Val Val
 85 90 95
 ccn ggn ccn aar aar gcn ccn atg gay wsn ytn tty gay tay ggn acn 336
 Pro Gly Pro Lys Lys Ala Pro Met Asp Ser Leu Phe Asp Tyr Gly Thr
 100 105 110
 tay mgn cay cay wsn wsn gay aay aar mgn tgg mgn aar aar ath ath 384
 Tyr Arg His His Ser Ser Asp Asn Lys Arg Trp Arg Lys Lys Ile Ile
 115 120 125
 gar aar car ccn car wsn ccn aar gcn ccn gcn ccn car ccn ccn ccn 432
 Glu Lys Gln Pro Gln Ser Pro Lys Ala Pro Ala Pro Gln Pro Pro Pro

130	135	140	
ath ytn aar gtn tty aay mgn ccn ath ytn tty gay ath gtn wsn mgn Ile Leu Lys Val Phe Asn Arg Pro Ile Leu Phe Asp Ile Val Ser Arg 145 150 155 160			480
ggn wsn acn gcn gay ytn gay ggn ytn ytn ccn tty ytn ytn acn cay Gly Ser Thr Ala Asp Leu Asp Gly Leu Leu Pro Phe Leu Leu Thr His 165 170 175			528
aar aar mgn ytn acn gay gar gar tty mgn gar ccn wsn acn ggn aar Lys Lys Arg Leu Thr Asp Glu Glu Phe Arg Glu Pro Ser Thr Gly Lys 180 185 190			576
acn tgy ytn ccn aar gcn ytn ytn aay ytn wsn aay ggn mgn aay gay Thr Cys Leu Pro Lys Ala Leu Leu Asn Leu Ser Asn Gly Arg Asn Asp 195 200 205			624
acn ath ccn gtn ytn ytn gay ath gcn gar mgn acn ggn aay atg mgn Thr Ile Pro Val Leu Leu Asp Ile Ala Glu Arg Thr Gly Asn Met Arg 210 215 220			672
gar tty ath aay wsn ccn tty mgn gay ath tay tay mgn ggn car acn Glu Phe Ile Asn Ser Pro Phe Arg Asp Ile Tyr Tyr Arg Gly Gln Thr 225 230 235 240			720
gcn ytn cay ath gcn ath gar mgn mgn tgy aar cay tay gtn gar ytn Ala Leu His Ile Ala Ile Glu Arg Arg Cys Lys His Tyr Val Glu Leu 245 250 255			768
ytn gtn gcn car ggn gcn gay gtn cay gcn car gcn mgn ggn mgn tty Leu Val Ala Gln Gly Ala Asp Val His Ala Gln Ala Arg Gly Arg Phe 260 265 270			816
tty car ccn aar gay gar ggn ggn tay tty tay tty ggn gar ytn ccn Phe Gln Pro Lys Asp Glu Gly Gly Tyr Phe Tyr Phe Gly Glu Leu Pro 275 280 285			864
ytn wsn ytn gcn gcn tgy acn aay car ccn cay ath gtn aay tay ytn Leu Ser Leu Ala Ala Cys Thr Asn Gln Pro His Ile Val Asn Tyr Leu 290 295 300			912
acn gar aay ccn cay aar aar gcn gay atg mgn mgn car gay wsn mgn Thr Glu Asn Pro His Lys Lys Ala Asp Met Arg Arg Gln Asp Ser Arg 305 310 315 320			960
ggn aay acn gtn ytn cay gcn ytn gtn gcn ath gcn gay aay acn mgn Gly Asn Thr Val Leu His Ala Leu Val Ala Ile Ala Asp Asn Thr Arg 325 330 335			1008
gar aay acn aar tty gtn acn aar atg tay gay ytn ytn ytn ytn aar Glu Asn Thr Lys Phe Val Thr Lys Met Tyr Asp Leu Leu Leu Leu Lys 340 345 350			1056
tgy gcn mgn ytn tty ccn gay wsn aay ytn gar gcn gtn ytn aay aay Cys Ala Arg Leu Phe Pro Asp Ser Asn Leu Glu Ala Val Leu Asn Asn 355 360 365			1104
gay ggn ytn wsn ccn ytn atg atg gcn gcn aar acn ggn aar ath ggn Asp Gly Leu Ser Pro Leu Met Met Ala Ala Lys Thr Gly Lys Ile Gly 370 375 380			1152
ath tty car cay ath ath mgn mgn gar gtn acn gay gar gay acn mgn Ile Phe Gln His Ile Ile Arg Arg Glu Val Thr Asp Glu Asp Thr Arg 385 390 395 400			1200
cay ytn wsn mgn aar tty aar gay tgg gcn tay ggn ccn gtn tay wsn His Leu Ser Arg Lys Phe Lys Asp Trp Ala Tyr Gly Pro Val Tyr Ser			1248

58/75

405				410				415								
wsn	ytn	tay	gay	ytn	wsn	wsn	ytn	gay	acn	tgy	ggn	gar	gar	gcn	wsn	1296
Ser	Leu	Tyr	Asp	Leu	Ser	Ser	Leu	Asp	Thr	Cys	Gly	Glu	Glu	Ala	Ser	
			420					425						430		
gtn	ytn	gar	ath	ytn	gtn	tay	aay	wsn	aar	ath	gar	aay	mgn	cay	gar	1344
Val	Leu	Glu	Ile	Leu	Val	Tyr	Asn	Ser	Lys	Ile	Glu	Asn	Arg	His	Glu	
		435					440					445				
atg	ytn	gcn	gtn	gar	ccn	ath	aay	gar	ytn	ytn	mgn	gay	aar	tgg	mgn	1392
Met	Leu	Ala	Val	Glu	Pro	Ile	Asn	Glu	Leu	Leu	Arg	Asp	Lys	Trp	Arg	
	450					455					460					
aar	tty	ggn	gcn	gtn	wsn	tty	tay	ath	aay	gtn	gtn	wsn	tay	ytn	tgy	1440
Lys	Phe	Gly	Ala	Val	Ser	Phe	Tyr	Ile	Asn	Val	Val	Ser	Tyr	Leu	Cys	
465					470					475					480	
gcn	atg	gtn	ath	tty	acn	ytn	acn	gcn	tay	tay	car	ccn	ytn	gar	ggn	1488
Ala	Met	Val	Ile	Phe	Thr	Leu	Thr	Ala	Tyr	Tyr	Gln	Pro	Leu	Glu	Gly	
			485						490					495		
acn	ccn	ccn	tay	ccn	tay	mgn	acn	acn	gtn	gay	tay	ytn	mgn	ytn	gcn	1536
Thr	Pro	Pro	Tyr	Pro	Tyr	Arg	Thr	Thr	Val	Asp	Tyr	Leu	Arg	Leu	Ala	
			500					505					510			
ggn	gar	gtn	ath	acn	ytn	tty	acn	ggn	gtn	ytn	tty	tty	tty	acn	aay	1584
Gly	Glu	Val	Ile	Thr	Leu	Phe	Thr	Gly	Val	Leu	Phe	Phe	Phe	Thr	Asn	
		515					520					525				
ath	aar	gay	ytn	tty	atg	aar	aar	tgy	ccn	ggn	gtn	aay	wsn	ytn	tty	1632
Ile	Lys	Asp	Leu	Phe	Met	Lys	Lys	Cys	Pro	Gly	Val	Asn	Ser	Leu	Phe	
	530					535					540					
ath	gay	ggn	wsn	tty	car	ytn	ytn	tay	tty	ath	tay	wsn	gtn	ytn	gtn	1680
Ile	Asp	Gly	Ser	Phe	Gln	Leu	Leu	Tyr	Phe	Ile	Tyr	Ser	Val	Leu	Val	
545					550					555					560	
ath	gtn	wsn	gcn	gcn	ytn	tay	ytn	gcn	ggn	ath	gar	gcn	tay	ytn	gcn	1728
Ile	Val	Ser	Ala	Ala	Leu	Tyr	Leu	Ala	Gly	Ile	Glu	Ala	Tyr	Leu	Ala	
			565						570					575		
gtn	atg	gtn	tty	gcn	ytn	gtn	ytn	ggn	tgg	atg	aay	gcn	ytn	tay	tty	1776
Val	Met	Val	Phe	Ala	Leu	Val	Leu	Gly	Trp	Met	Asn	Ala	Leu	Tyr	Phe	
			580					585					590			
acn	mgn	ggn	ytn	aar	ytn	acn	ggn	acn	tay	wsn	ath	atg	ath	car	aar	1824
Thr	Arg	Gly	Leu	Lys	Leu	Thr	Gly	Thr	Tyr	Ser	Ile	Met	Ile	Gln	Lys	
		595					600					605				
ath	ytn	tty	aar	gay	ytn	tty	mgn	tty	ytn	ytn	gtn	tay	ytn	ytn	tty	1872
Ile	Leu	Phe	Lys	Asp	Leu	Phe	Arg	Phe	Leu	Leu	Val	Tyr	Leu	Leu	Phe	
	610					615					620					
atg	ath	ggn	tay	gcn	wsn	gcn	ytn	gtn	wsn	ytn	ytn	aay	ccn	tgy	gcn	1920
Met	Ile	Gly	Tyr	Ala	Ser	Ala	Leu	Val	Ser	Leu	Leu	Asn	Pro	Cys	Ala	
625					630					635					640	
aay	atg	aar	gtn	tgy	aay	gar	gay	car	acn	aay	tgy	acn	gtn	ccn	acn	1968
Asn	Met	Lys	Val	Cys	Asn	Glu	Asp	Gln	Thr	Asn	Cys	Thr	Val	Pro	Thr	
			645						650					655		
tay	ccn	wsn	tgy	mgn	gay	wsn	gar	acn	tty	wsn	acn	tty	ytn	ytn	gay	2016
Tyr	Pro	Ser	Cys	Arg	Asp	Ser	Glu	Thr	Phe	Ser	Thr	Phe	Leu	Leu	Asp	
			660					665					670			
ytn	tty	aar	ytn	acn	ath	ggn	atg	ggn	gay	ytn	gar	atg	ytn	wsn	wsn	2064
Leu	Phe	Lys	Leu	Thr	Ile	Gly	Met	Gly	Asp	Leu	Glu	Met	Leu	Ser	Ser	

59/75

675				680				685								
acn	aar	tay	ccn	gtn	gtn	tty	ath	ath	ytn	ytn	gtn	acn	tay	ath	ath	2112
Thr	Lys	Tyr	Pro	Val	Val	Phe	Ile	Ile	Leu	Leu	Val	Thr	Tyr	Ile	Ile	
690				695				700								
ytn	acn	tty	gtn	ytn	ytn	ytn	aay	atg	ytn	ath	gcn	ytn	atg	ggn	gar	2160
Leu	Thr	Phe	Val	Leu	Leu	Leu	Asn	Met	Leu	Ile	Ala	Leu	Met	Gly	Glu	
705				710				715				720				
acn	gtn	ggn	car	gtn	wsn	aar	gar	wsn	aar	cay	ath	tgg	aar	ytn	car	2208
Thr	Val	Gly	Gln	Val	Ser	Lys	Glu	Ser	Lys	His	Ile	Trp	Lys	Leu	Gln	
725				730				735								
tgg	gcn	acn	acn	ath	ytn	gay	ath	gar	mgn	wsn	tty	ccn	gtn	tty	ytn	2256
Trp	Ala	Thr	Thr	Ile	Leu	Asp	Ile	Glu	Arg	Ser	Phe	Pro	Val	Phe	Leu	
740				745				750								
mgn	aar	gcn	tty	mgn	wsn	ggn	gar	atg	gtn	acn	gtn	ggn	aar	wsn	wsn	2304
Arg	Lys	Ala	Phe	Arg	Ser	Gly	Glu	Met	Val	Thr	Val	Gly	Lys	Ser	Ser	
755				760				765								
gay	ggn	acn	ccn	gay	mgn	mgn	tgg	tgy	tty	mgn	gtn	gay	gar	gtn	aay	2352
Asp	Gly	Thr	Pro	Asp	Arg	Arg	Trp	Cys	Phe	Arg	Val	Asp	Glu	Val	Asn	
770				775				780								
tgg	wsn	cay	tgg	aay	car	aay	ytn	ggn	ath	ath	aay	gar	gay	ccn	ggn	2400
Trp	Ser	His	Trp	Asn	Gln	Asn	Leu	Gly	Ile	Ile	Asn	Glu	Asp	Pro	Gly	
785				790				795				800				
aar	aay	gar	acn	tay	car	tay	tay	ggn	tty	wsn	cay	acn	gtn	ggn	mgn	2448
Lys	Asn	Glu	Thr	Tyr	Gln	Tyr	Tyr	Gly	Phe	Ser	His	Thr	Val	Gly	Arg	
805				810				815								
ytn	mgn	mgn	gay	mgn	tgg	wsn	wsn	gtn	gtn	ccn	mgn	gtn	gtn	gar	ytn	2496
Leu	Arg	Arg	Asp	Arg	Trp	Ser	Ser	Val	Val	Pro	Arg	Val	Val	Glu	Leu	
820				825				830								
aay	aar	aay	wsn	aay	ccn	gay	gar	gtn	gtn	gtn	ccn	ytn	gay	wsn	atg	2544
Asn	Lys	Asn	Ser	Asn	Pro	Asp	Glu	Val	Val	Val	Pro	Leu	Asp	Ser	Met	
835				840				845								
ggn	aay	ccn	mgn	tgy	gay	ggn	cay	car	car	ggn	tay	ccn	mgn	aar	tgg	2592
Gly	Asn	Pro	Arg	Cys	Asp	Gly	His	Gln	Gln	Gly	Tyr	Pro	Arg	Lys	Trp	
850				855				860								
mgn	acn	gar	gay	gcn	ccn	ytn										2613
Arg	Thr	Glu	Asp	Ala	Pro	Leu										
865				870												

<210> 19

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide probe that hybridizes to mouse
TRPV3-encoding nucleic acid

<400> 19

tgacatgatc ctgctgagga gtg

23

<210> 20

<211> 22

<212> DNA

<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 20
acgaggcagg cgaggtattc tt 22

<210> 21
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 21
cagcgtatgc agaggctcca gggtcag 27

<210> 22
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 22
ttgaagtcct cagccaccgt cacca 25

<210> 23
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 23
caccagcgcg tgcaggatgt 20

<210> 24
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 24
tcgttctcct cagcgaaggc aagcaga 27

<210> 25
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 25
ccttctatct ccaggaagaa gtgtgc 26

<210> 26
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 26
gtcaccagcg cgtgcaggat gttgt 25

<210> 27
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 27
aggcccatag gccagtcgc tgaac 25

<210> 28
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 28
catgccata gactggaagc c 21

<210> 29
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 29
gatggcgatg ttcagcgctg tctgc 25

<210> 30
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 30
gctgccaaga tgggcaaggc tgaga 25

<210> 31
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 31
cctgggctgg gcgaacatgc tcta 24

<210> 32
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 32

gcgccagatg cgttcacttt ctttgga 27

<210> 33
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 33
tgacatgatc ctgctgagga gtg 23

<210> 34
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 34
acgaggcagg cgaggtattc tt 22

<210> 35
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 35
tccaagctgt gcttgtgata 20

<210> 36
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 36
cttgagcatg tagtttcaca caaa 24

<210> 37
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 37
gtgtttttcca ttccgtccac 20

<210> 38
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 38
cgacgtttct gggaattcat 20

<210> 39
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 39
cttgagcatg tagtttcaca caaa 24

<210> 40
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 40
tcctcctcct caacatgctc 20

<210> 41
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 41
tggaatcaa aacagtattt caatg 25

<210> 42
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 42
ctcttcaagc tcacatagg c 21

<210> 43
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 43
cgacgtttct gggaattcat 20

<210> 44
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 44
gtgttttcca ttccgtccac 20

<210> 45
<211> 20

<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 45
ccctctgtta ccgcagacac 20

<210> 46
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 46
actccagcct gggtgaca 18

<210> 47
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 47
atggtctcca gctcccagtt 20

<210> 48
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 48
aggaggacga aggtgaggat 20

<210> 49
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 49
agcctcaggt ctgaagtgga 20

<210> 50
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 50
gccagatgcg ttcactttct 20

<210> 51
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 51
ggcaaatttc ttccatttcg 20

<210> 52
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 52
agatgcgttc gctctcctt 19

<210> 53
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 53
tgcacacttc ttcttgagga t 21

<210> 54
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 54
ttctcatgc acaagctgac 20

<210> 55
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 55
tcttcttgga gatagaaggg att 23

<210> 56
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 56
cgatgatttc cagcacagag 20

<210> 57
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 57

ctcaccaatg tagacacaac gac

23

<210> 58

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 58

taccagcatg aaggcttcta ttt

23

<210> 59

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 59

ataagcactg ctgtgatgtc tcc

23

<210> 60

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 60

gtcagcttgt gcatgaggaa

20

<210> 61

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 61

tgacagagac cccatccaat cccaaca

27

<210> 62

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 62

ctcttgatg atggctttct gg

22

<210> 63

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 63
gagaaggagt gggtgagctg 20

<210> 64
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 64
ccttctccca gagtccacag 20

<210> 65
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 65
agcaggcagg aaaatgagag 20

<210> 66
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 66
ccaaagatgg tccagaaagc 20

<210> 67
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 67
ctcttgtgat atggctttct gg 22

<210> 68
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 68
aactgtgatg acatggactc tccccag 28

<210> 69
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 69
aactgtgatg acatggactc 20

<210> 70
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 70
caggatgatg tgacagagac cccatc 26

<210> 71
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 71
atgatcctgc tgaggagtgg 20

<210> 72
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 72
aggatgacac aggcccatc 20

<210> 73
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 73
atcctcacct tcgtcctcct 20

<210> 74
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 74
cattccgtcc acttcacctc 20

<210> 75
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 75
tggttttgct gttgttcctg 20

<210> 76

<211> 23
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Oligonucleotide primer

<400> 76
 catgtaaatc aacgcagaag tca

23

<210> 77
 <211> 20
 <212> PRT
 <213> Mus musculus

<400> 77
 Cys Asp Asp Met Asp Ser Pro Gln Ser Pro Gln Asp Asp Val Thr Glu
 1 5 10 15
 Thr Pro Ser Asn
 20

<210> 78
 <211> 14
 <212> PRT
 <213> Mus musculus

<400> 78
 Lys Ile Gln Asp Ser Ser Arg Ser Asn Ser Lys Thr Thr Leu
 1 5 10

<210> 79
 <211> 22
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Oligonucleotide primer

<400> 79
 ctcatgcaca agctgacagc ct

22

<210> 80
 <211> 26
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Oligonucleotide primer

<400> 80
 aggctcttc cgtgtactca gcgttg

26

<210> 81
 <211> 23
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Oligonucleotide primer

<400> 81
 atctggcacc acaccttcta caa

23

<210> 82
 <211> 20
 <212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 82
gccagccagg tccagacgca 20

<210> 83
<211> 22
<212> DNA
<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 83
ctcatgcaca agctgacagc ct 22

<210> 84
<211> 26
<212> DNA
<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 84
aggcctcttc cgtgtactca gcgttg 26

<210> 85
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 85
ccctgggctg ggcgaacatg ctcta 25

<210> 86
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 86
cttggcagcc atcatgagag gcgaa 25

<210> 87
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Oligonucleotide primer

<400> 87
gcagtggtaa caacgcagag 20

<210> 88
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 88
aggtcagatc tgtggcaggt 20

<210> 89
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 89
cgtgaggtga cagatgagga 20

<210> 90
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 90
ccagtatggc agatcctggg 20

<210> 91
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 91
atggcagatc ctggtgatg 19

<210> 92
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 92
cccaggcact actgaggact 20

<210> 93
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 93
agggctacgc tcccaagt 18

<210> 94
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 94
gtgctggctt aggtgactcc 20

<210> 95
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 95
tgaggatgac ataggtgatg ag 22

<210> 96
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 96
ccaaggacaa aaaggactgc 20

<210> 97
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 97
caagtttgtc cgctcttttc 20

<210> 98
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 98
aactgtctgg agctggcagt 20

<210> 99
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 99
caagtttgtc cgctcttttc 20

<210> 100
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 100

actgccagct ccagacagtt 20

<210> 101
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 101
ccttcgatgt gctggctctg ggcataa 27

<210> 102
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 102
ccttgcccttt cttccccaga gtctcaa 27

<210> 103
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 103
gcaaagtttt tggctccacc cgtca 25

<210> 104
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 104
gccagtgctg ggtcagcagt tcgta 25

<210> 105
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 105
ttcaggaggt catgttcacg gctctca 27

<210> 106
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 106
gtaccggaac ctgcagatcg ccaaga 26

<210> 107
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 107
gcaagatccc ttgtgtggtg gtgga 25

<210> 108
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 108
cagcctggtg gaggtggagg atggt 25

<210> 109
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 109
cggaacctgc agatcgccaa gaact 25

<210> 110
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 110
gcgtggccag acaggggatc ctaag 25

<210> 111
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 111
ccacacagca aagaggaaca 20

<210> 112
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 112
ggagccgcag aaatgtact 20

<210> 113
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 113
tctcattggc ctcatttctg 20

<210> 114
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide primer

<400> 114
atatgagacc cgagcagtgg 20

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/101045 A3

(51) International Patent Classification⁷: **C12N 15/12**,
C07K 14/705, C12N 5/10, C12Q 1/68, C07K 16/18,
G01N 33/50, 33/53

(21) International Application Number: PCT/EP02/06520

(22) International Filing Date: 13 June 2002 (13.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/297,835	13 June 2001 (13.06.2001)	US
60/351,238	22 January 2002 (22.01.2002)	US
60/352,914	29 January 2002 (29.01.2002)	US
60/357,161	12 February 2002 (12.02.2002)	US
60/381,086	15 May 2002 (15.05.2002)	US
60/381,739	16 May 2002 (16.05.2002)	US

(71) Applicants (for all designated States except US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH). **IRM LLC** [US/—]; PO Box HM 2899, Hamilton HM LX (BM).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PATAPOUTIAN, Ardem** [US/US]; 4330 North Talmadge Drive, San Diego, CA 92116 (US). **SONG, Chuangzheng** [CN/US]; 87 Reinman Road, Warren, NJ 07059 (US). **GANJU, Pamposh** [GB/GB]; Novartis Institute for Medical Sciences, University College, 5 Gower Place, London WC1E 6BN (GB). **PEIER, Andrea** [US/US]; 9725 Mesa Springs

Way 176, San Diego, CA 92126 (US). **MCINTYRE, Peter** [AU/GB]; Novartis Institute for Medical Sciences, University College, 5 Gower Place, London WC1E 6BN (GB). **BEVAN, Stuart** [GB/GB]; Novartis Institute for Medical Sciences, University College, 5 Gower Place, London WC1E 6BN (GB).

(74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:

— with international search report

(88) Date of publication of the international search report:
20 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: VANILLOID RECEPTOR-RELATED NUCLEIC ACIDS AND POLYPEPTIDES

(57) Abstract: This invention provides novel genes and polypeptides of the VR family, identification of trkA⁺ pain specific genes expressed in the DRG, and use of these genes and polypeptides for the treatment of pain and identification of agents useful in the treatment of pain.

WO 02/101045 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/06520

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/12 C07K14/705 C12N5/10 C12Q1/68 C07K16/18 G01N33/50 G01N33/53		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K C12N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) BIOSIS, MEDLINE, WPI Data, EPO-Internal, FSTA, EMBASE, PAJ, EMBL		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CATERINA M J ET AL: "THE CAPSAICIN RECEPTOR: A HEAT-ACTIVATED ION CHANNEL IN THE PAIN PATHWAY" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 389, 23 October 1997 (1997-10-23), pages 816-824, XP002075020 ISSN: 0028-0836 the whole document See especially Figure 5a -& DATABASE EMBL 'Online! 30 October 1997 (1997-10-30) "Rattus norvegicus vanilloid receptor subtype 1 mRNA, complete cds" retrieved from EMBL Database accession no. AF029310 XP002239516 the whole document <div style="text-align: center;">---</div> <div style="text-align: center;">-/--</div>	1,2,12, 13, 15-17, 19-21
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search	Date of mailing of the international search report	
3 July 2003	13.08.03	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Turri, M	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/06520

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	PEIER ANDREA M ET AL: "A heat-sensitive TRP channel expressed in keratinocytes." SCIENCE (WASHINGTON D C), vol. 296, no. 5575, 2002, pages 2046-2049, XP002239399 14 June, 2002 ISSN: 0036-8075	1-50, 145-168
T	-& DATABASE EMBL 'Online! 6 April 2003 (2003-04-06) "Homo sapiens transient receptor potential cation channel, subfamily V, member 3 (TRPV3), mRNA" retrieved from EMBL Database accession no. NM_145068 XP002239517 the whole document	
T	-& DATABASE EMBL 'Online! 6 April 2003 (2003-04-06) "Mus musculus transient receptor potential cation channel, subfamily V, member 3 (Trpv3), mRNA" retrieved from EMBL Database accession no. NM_145099 XP002239518 the whole document	
T	--- XU HAOXING ET AL: "TRPV3 is a calcium-permeable temperature-sensitive cation channel." NATURE (LONDON), vol. 418, no. 6894, 2002, pages 181-186, XP002239400 11 July, 2002 ISSN: 0028-0836	1-50, 145-168
T	--- SMITH G D ET AL: "TRPV3 is a temperature-sensitive vanilloid receptor-like protein." NATURE (LONDON), vol. 418, no. 6894, 2002, pages 186-190, XP002239401 11 July, 2002 ISSN: 0028-0836 --- -/--	1-50, 145-168

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/06520

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TSVALER LARISA ET AL: "Trp-p8, a novel prostate-specific gene, is up-regulated in prostate cancer and other malignancies and shares high homology with transient receptor potential calcium channel proteins."</p> <p>CANCER RESEARCH, vol. 61, no. 9, 1 May 2001 (2001-05-01), pages 3760-3769, XP002246273 ISSN: 0008-5472 the whole document</p> <p>See especially Page 3763, Fig. 1</p>	97-129, 134-168
T	<p>-& DATABASE EMBL 'Online! 13 April 2002 (2002-04-13) TSVALER, L. ET AL.: "Homo sapiens transient receptor potential cation channel protein (TRPM8) mRNA, complete cds" retrieved from EMBL Database accession no. AY090109 XP002246300 the whole document</p>	
X	<p>US 6 194 152 B1 (SHAPERO MICHAEL H ET AL) 27 February 2001 (2001-02-27) See sequences 14 and 15</p>	97-129, 134-168
T	<p>PEIER ANDREA M ET AL: "A TRP channel that senses cold stimuli and menthol." CELL, vol. 108, no. 5, 8 March 2002 (2002-03-08), pages 705-715, XP002246274 March 8, 2002 ISSN: 0092-8674</p>	97-129, 134-168
T	<p>-& DATABASE EMBL 'Online! 15 May 2002 (2002-05-15) PATAPOUTIAN, A. AND PEIER, A.M.: "Musculus TRP ion channel TRPM8 (Trpm8) mRNA, complete cds" retrieved from EMBL Database accession no. AF481480 XP002246301 the whole document</p>	
T	<p>FUESSEL SUSANNE ET AL: "Multiple tumor marker analyses (PSA, hK2, PSCA, trp-p8) in primary prostate cancers using quantitative RT-PCR." INTERNATIONAL JOURNAL OF ONCOLOGY. GREECE JUL 2003, vol. 23, no. 1, July 2003 (2003-07), pages 221-228, XP009013243 ISSN: 1019-6439</p>	97-129, 134-168

	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/06520

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CLAPHAM D E ET AL: "The TRP ion channel family." NATURE REVIEWS. NEUROSCIENCE. ENGLAND JUN 2001, vol. 2, no. 6, 1 June 2001 (2001-06-01), pages 387-396, XP001135189 ISSN: 1471-003X page 391; table 1 ----	
T	MONTELL CRAIG ET AL: "A unified nomenclature for the superfamily of TRP cation channels." MOLECULAR CELL, vol. 9, no. 2, February 2002 (2002-02), pages 229-231, XP002239402 February, 2002 ISSN: 1097-2765 ----	
T	PENG JI-BIN ET AL: "Structural conservation of the genes encoding CaT1, CaT2, and related cation channels." GENOMICS, vol. 76, no. 1-3, August 2001 (2001-08), pages 99-109, XP002239515 ISSN: 0888-7543 -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/06520

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 40-50 and 134-144 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 36-39, 130-133, 166
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-50, 97-129, 134-144 (completely), 145-168 (partially)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-50 (completely), 145-168 (partially)

Murine and human TRPV3 receptors (SEQ ID NOs:1-6)
Polynucleotides encoding the receptors. Host cells.
Polypeptides. Antibodies. Methods for identifying agents that modulate cation passage through a membrane. Methods for reducing pain associated with said receptors. Methods for determining whether pain in a subject is mediated by said receptor.

Methods for identifying agents useful in the modulation of a mammalian sensory response. Methods for monitoring the efficacy of a treatment on a subject suffering from pain. Assays capable of detecting the expression of said receptors. Methods for treating pain. Methods for identifying agents useful in the treatment of pain. Methods for identifying agents that bind and/or modulates the activity of said receptor.

2. Claims: 51-96 (completely), 145-168 (partially)

As Group 1, but with Murine TRPV4 (SEQ ID NOs:13-15)

3. Claims: 51-96 (completely), 145-168 (partially)

As Group 1, but with Human TRPV4 (SEQ ID NOs:16-18)

4. Claims: 97-144 (completely), 145-168 (partially)

As Group 1, but with Murine TRPM8 (SEQ ID NOs:7-9)

5. Claims: 97-144 (completely), 145-168 (partially)

As Group 1, but with Human TRPM8 (SEQ ID NOs:10-12)

Continuation of Box I.2

Claims Nos.: 36-39, 130-133, 166

Present claims 36-39, 130-133 and 166 relate to a compound defined by reference to a desirable characteristic or property, namely:

reducing the TRPV3- or TRPM8-mediated cation passage through a membrane or reducing signal transduction from a TRPV3 or TRPM8 polypeptide to a DRG neuron (claims 36 and 130); inhibiting the TRPV3 or TRPM8 polypeptides (claim 166).

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to ruthenium red mentioned in the description at pages 69, lines 21-23 as an inhibitor of the TRPV3 polypeptide.

No inhibitors of the TRPM8 polypeptide are disclosed in the application. Consequently, claims 130-133 and 166 (as relating to TRPM8) have not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/06520

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6194152	B1	27-02-2001	AU 744875 B2	07-03-2002
			AU 9021898 A	08-03-1999
			CA 2300364 A1	25-02-1999
			EP 1005549 A2	07-06-2000
			JP 2001514889 T	18-09-2001
			NZ 503404 A	01-03-2002
			WO 9909166 A2	25-02-1999
<hr/>				

This Page Blank (uspto)